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Auditory Cortical Projections to the Cat Inferior Colliculus

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ABSTRACT

The projection from 11 auditory cortical areas onto the subdivisions of the inferior colliculus was studied in adult cats by using two different anterograde tracers to label corticocollicular (CC) axon terminals. The main results were that: 1) a significant CC projection arose from every field; 2) the principal inferior collicular targets were the dorsal cortex, lateral nucleus, caudal cortex, and intercollicular tegmentum, with only a sparse projection to the central nucleus; 3) the input was usually bilateral, with the ipsilateral side by far the most heavily labeled, and the contralateral projection was a symmetrical subset of the ipsilateral input; 4) the CC system is both divergent and convergent, with single cortical areas projecting to six or more collicular subdivisions, and each auditory midbrain subdivision receiving a convergent projection from two to ten cortical areas; 5) cortical areas devoid of tonotopic organization have topographic projections to collicular target nuclei; 6) the heaviest CC projection terminated in the caudal half of the inferior colliculus; and finally, 7) the relative strength of the corticocollicular labeling was far less than that of the corresponding corticothalamic projection in the same experiments.

The CC system is strategically placed to influence both descending and ascending pathways arising in the inferior colliculus. Nuclei that participate in the premotor system, like the inferior collicular subdivisions that project to the pons, receive substantial corticofugal input. Both the dorsal (pericentral) and the lateral (external) nuclei of the inferior colliculus project to parts of the medial geniculate body whose closest auditory affiliations are with nontonotopic cortical regions involved in higher order auditory perception. The corticocollicular system may link brainstem and colliculothalamic circuits to coordinate premotor and perceptual aspects of hearing. J. Comp. Neurol. 400:147–174, 1998.

Indexing terms: corticocollicular; corticofugal; corticotectal; auditory system; midbrain

The inferior colliculus (IC) is one of the first sites in the auditory pathway that receives substantial descending input from the auditory cortex as well as ascending projections from acoustic nuclei in the medulla and pons (Aitkin, 1986). This convergence provides the initial opportunity for interactions between streams of information that represent peripheral events with great fidelity (the ascending channel) and centers involved in higher-order processing (the descending stream). In the corticofugal system, the many synapses between the periphery and the cerebral cortex imply that much of the precise spatial and temporal information initially encoded by the brainstem is transformed and redistributed. The corticocollicular projection (CC) permits prospective cortical access to any or all of the four main classes of projection that arise in the IC. These consist of 1) descending systems (tectopontine, tectomedullary, and tectoreticular; Hashikawa, 1983); 2) the commissural pathway linking the inferior colliculi (Aitkin and Phillips, 1984); 3) the intrinsic and ipsilateral projections (Oliver et al., 1991; Saldaña and Merchán, 1992), and 4) the tectothalamic input (Morest, 1965; Andersen et al., 1980a). The enormous range of function in both the sensory and premotor domains that such projections might influence is an indirect measure of their importance.

The goal of the present studies is to provide a clearer and more complete picture of the distribution, topography, and axonal structure of the feline auditory CC system using sensitive and specific tracers. This provides the context for a parallel analysis of the corticothalamic projection and it will serve as a framework for contrasting the organiza-

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tional principles of these and other corticofugal systems. In the motor cortex, for example, pyramidal neurons influence spinal motoneuronal discharge and exert an executive effect on the control of voluntary movement (Phillips and Porter, 1977). No analogous functional role exists for these sensory corticofugal projections, which are comparable in size and connectional divergence to their motor counterparts (Frigyesi et al., 1972).

We address three chief questions in this study. First, is there a nuclear or a spatial segregation of CC input or do projections from functionally affiliated cortical areas converge in the midbrain? Since the ascending input to IC from the cochlear nucleus (Osen, 1972; Oliver, 1984) and the superior olivary complex (Glendenning and Masterton, 1983) targets particular IC subdivisions topographically, perhaps corticofugal projections have similar specificity. Prior work could not resolve this issue since large cortical ablations and silver degeneration methods (Diamond et al., 1969) lack the spatial resolution available with contemporary axoplasmic transport or axonal bulk-filling methods. More recent studies with tritium autoradiography (Andersen et al., 1980b) produced equivocal results with regard to fine projections or even failed to reveal some inputs demonstrated with other methods (Sousa-Pinto and Reis, 1975). A related goal is to extend our observations to the 11 areas we have included within the rubric of auditory cortex and to compare their differential patterns of input to the auditory midbrain and thalamus (Winer, 1992).

A second question is the nature of terminal divergence within the IC. Do individual tonotopic fields project to more than one IC division? Do these fields have the same topography of projection to nuclei with, or devoid of, tonotopic organization? Although cortical areas with a tonotopic representation usually project topographically, it is unclear if this rule extends to the many areas without such an organization. Although the inferior collicular targets of AI and AII have been described (Andersen et al., 1980b), the CC inputs from periauditory fields that adjoin visual (Bowman and Olson, 1988a,b) and limbic (Fallon et al., 1978) association areas remain to be considered. These results may have different consequences for the descending control of the midbrain.

The third issue is whether parallel corticofugal inputs from various areas reach different subdivisions of the IC. It is now widely accepted that the ascending auditory, visual, and somatic sensory systems each contain independent channels that are distinguished readily on the bases of receptor diversity, physiological organization, and axonal branching. It seems timely to attempt to extend this proposition to the corticofugal system and to evaluate the logic of its connectional targets. Given the richness of commissural (Aitkin and Phillips, 1984) and internuclear (Oliver et al., 1991) projections in the IC and the virtual absence of comparable circuits in the medial geniculate body (unpublished observations), such data on the CC projection can contribute to a clearer picture of how descending pathways influence subcortical targets selectively. This can lead to the formation of more explicit hypotheses about the principles of organization and the differential actions of the corticocollicular and corticothalamic systems (King, 1997). A preliminary report has appeared (Hefti et al., 1995).

Abbreviations

AAF	anterior auditory field
AI	primary auditory cortex
AII	second auditory cortical area
ALLS	anterior lateral lateral suprasylvian area
AMLS	anterior medial lateral suprasylvian area
BIC	brachium of the inferior colliculus
BICN	nucleus of the brachium of the inferior colliculus
BSC	brachium of the superior colliculus
CC	caudal cortex of the inferior colliculus
CG	central gray
CIC	commissure of the inferior colliculus
Cl	claustrum
CN	central nucleus of the inferior colliculus
Cu	cuneiform nucleus
D	dorsal nucleus of the medial geniculate body
DC	dorsal cortex of the inferior colliculus
DCa	caudal dorsal nucleus of the medial geniculate body
DD	deep dorsal nucleus of the medial geniculate body
DNLL	dorsal nucleus of the lateral lemniscus
DS	dorsal superficial nucleus of the medial geniculate body
EP	posterior ectosylvian gyrus
EPD	posterior ectosylvian gyrus, dorsal part
EPI	posterior ectosylvian gyrus, intermediate part
EPV	posterior ectosylvian gyrus, ventral part
IC	inferior colliculus
IcT	intercollicular tegmentum
INLL	intermediate nucleus of the lateral lemniscus
Ins	insular cortex
LEA	lateral entorhinal area
LGB	lateral geniculate body
LL	lateral lemniscus
LN	lateral nucleus of the inferior colliculus
M	medial division of the medial geniculate body
MEA	medial entorhinal area
MGB	medial geniculate body
MLF	medial longitudinal fasciculus
MRF	mesencephalic reticular formation
OC	optic chiasm
OT	olfactory tubercle
Ov	*pars ovoidea* of the ventral division of the medial geniculate body
P	posterior auditory cortical area
PC	piriform cortex
PLLS	posterior lateral lateral suprasylvian area
PlZ	paralemniscal zone
PMLS	posterior medial lateral suprasylvian area
Pr	perirhinal cortex
Ra	raphe
RP	rostral pole nucleus of the inferior colliculus
Sa	sagulum
SC	superior colliculus
SCP	superior cerebellar peduncle
SCPX	decussation of the superior cerebellar peduncle
SF, SF/daz	suprasylvian fringe/dorsal auditory zone
SGI	intermediate gray layer of the superior colliculus
SGP	deep gray layer of the superior colliculus
SGS	superficial gray layer of the superior colliculus
Sgl	supragenicular nucleus, lateral part
Sgm	supragenicular nucleus, medial part
Te	temporal cortex
TM	mesencephalic trigeminal nucleus
Tr	trochlear nerve
V	ventral division of the medial geniculate body
Vb	ventrobasal complex
Ve	ventral auditory cortical area
Vl	ventrolateral nucleus of the medial geniculate body
VLEA	ventral lateral entorhinal area
VMEA	ventral medial entorhinal area
VP	ventral posterior auditory cortical area
I, II, III, IV	layers of the dorsal cortex of the inferior colliculus
5, 7, 18, 17, 19, 20a, 20b, 21a, 21b, 35, 36, SI, SII, SIII, SIV	nonauditory cortical areas
Planes of section:	
D	dorsal
M	medial
L	lateral
V	ventral

TABLE 1. Summary of Experiments

Area injected	Experiment	Tracer[1]	Volume	Survival (days)	Figures
AI	1324	5% WGA-HRP	0.2 μl	2	2A–C, 3
AI	1382 left	20% BDA	1.32 μl	6	
AI, AAF	1330	20% BDA	1.2 μl	15	2D
AI, SF	1283	5% WGA-HRP	0.6 μl	2	
AI, SF	JP48	5% WGA-HRP	0.1 μl	4	
AAF	1284	5% WGA-HRP	0.16 μl	1	
AAF	1309	10% BDA	0.6 μl	28	4
AAF	1381 right	20% BDA	0.88 μl	7	
AAF	1362	20% BDA	0.88 μl	8	
AAF, SI, VI	1334 right	20% BDA	1.2 μl	15	
P	1299	5% WGA-HRP	0.1 μl	4	5
P	1361	20% BDA	0.88 μl	8	6
P, SI, 17	1334 left	20% BDA	1.2 μl	15	
VP	1317	5% WGA-HRP	0.23 μl	3	
VP	1358	20% BDA	0.8 μl	8	12A
Ve	1297	5% WGA-HRP	0.08 μl	3	
AII	1325	5% WGA-HRP	0.2 μl	2	7, 12C
AII	1301	10% BDA	Iontophoresis	20	
AII	1383 left	20% BDA	1.32 μl	7	12B
AII	1376 left	20% BDA	0.88 μl	7	
AII, AI	1292	5% WGA-HRP	0.15 μl	2	
AII, 5, 19, 21a	1323 right	20% BDA	0.18 μl	19	
AII, SII, SIV, 18, 19	1323 left	20% BDA	Iontophoresis	19	
EPD	JP23	5% WGA-HRP	0.6 μl	4	
EPD	1371 left	20% BDA	0.88 μl	6	
EPI	1312	5% WGA-HRP	0.2 μl	3	8
EPV[2]	1313	5% WGA-HRP	0.2 μl	3	
Ins	1381 left	20% BDA	1.2 μl	7	12D
Ins	1336	5% WGA-HRP	0.2 μl	3	9
Ins	1333	5% WGA-HRP	0.2 μl	2	
Te	1224	5% WGA-HRP	0.6 μl	4	10
Te	1364	20% BDA	0.88 μl	7	
SF	JP44	5% WGA-HRP	0.8 μl	3	11
SF	1380 left	20% BDA	2.07 μl	6	
SF, AI	1217	5% WGA-HRP	1.2 μl	4	
18	1383 right	20% BDA	1.1 μl	7	
19	1371 right	20% BDA	1.32 μl	7	
20a, 20b, 21b	1376 right	20% BDA	1.32 μl	7	
SII	1380 right	20% BDA	1.15 μl	6	
SII, SIV	1365	20% BDA	0.88 μl	7	
5, 7	1382 right	20% BDA	0.88 μl	6	

[1]WGA-HRP, wheat germ agglutinin-horseradish peroxidase; BDA, biotinylated dextran amines.
[2]The inferior colliculus sections in this experiment were damaged in processing; the thalamus was intact and was retained for later analysis (Diehl and Winer, 1996).

MATERIALS AND METHODS

All procedures were approved by the appropriate institutional animal care and use committee. Postoperative care followed National Institutes of Health guidelines.

Wheat germ agglutinin conjugated to horseradish peroxidase (WGA-HRP) was used to label corticofugal axons projecting to the IC (Mesulam, 1978). A second series of experiments used biotinylated dextran amines (BDA) to bulk fill axons by diffusion (Brandt and Apkarian, 1992) and served to confirm the WGA-HRP studies. The particulars for all experiments appear in Table 1.

Surgery

Adult cats weighing 2.6–4.8 kg were used. Sterile surgeries were performed under isoflurane at a level (1–3%) sufficient to suppress all nociceptive reflexes and to achieve stage III, plane ii of general anesthesia. The animal was hydrated continuously with intravenous infusion of lactated Ringer's solution and maintained at 34–39°C on a heating pad. Respiration, arterial O_2, temperature, and electrocardiogram were monitored continuously; the level of anesthesia was adjusted accordingly to maintain areflexia. Cortical targets were located by sulcal landmarks related to electrophysiological and anatomical investigations (Reale and Imig, 1980).

Unilateral injections (1–2/animal) of 5% WGA-HRP (Sigma, St. Louis, MO) in sterile saline were made (Table 1). Penetrations were perpendicular to the cortical surface, and deposits were placed at different depths in a track to saturate all layers. A nanoliter hydraulic injector (World Precision Instruments, Sarasota, FL) ejected tracer through glass pipets (tip diameters: 35–50 μm). Pulses (4.6 or 9.2 nl/30–120 seconds) for 10–32 minutes delivered total volumes of 0.08–2.07 μl. In other experiments, BDA (3 K m.w.; Molecular Probes, Eugene, OR) dissolved in dH_2O was delivered by pressure or iontophoresis (BDA dissolved in saline) at concentrations of 10–20%. Volumes using pressure ranged from 0.18 to 1.3 μl. Survivals were 7–28 days, with the short and intermediate periods resulting in the most robust labeling. Buprenorphine (0.00875–0.0125 mg/kg, s.c.) was given postoperatively over the first 24 hours of survival.

Histology

Cats were reanesthetized with sodium pentobarbital (26 mg/kg, i.v.) and perfused transcardially. For WGA-HRP, the washout (0.12 M phosphate buffer [PB, pH 7.4], the vehicle in all subsequent procedures, with 0.001% lidocaine hydrochloride, 250–400 ml, 24°C) preceded the first fixative (0.5% paraformaldehyde/0.5% glutaraldehyde/PB, 1,000 ml, 4–10°C). This was followed by a stronger fixative (1% paraformaldehyde/1.5% glutaraldehyde, 2,250 ml, 4–10°C). For BDA, the procedure was as above, except that the fixative was 4% paraformaldehyde (pH 7.4). Cryoprotectant (10% sucrose, 500 ml) was perfused 1 hour later. The brain was blocked stereotaxically in the frontal plane, photographed, and placed in a second cryoprotectant solution (30% sucrose) for 1–3 days.

For WGA-HRP, frozen sections were cut at 60 μm. Three of each six were incubated with tetramethylbenzidine (TMB; Mesulam, 1978) and one of these was counterstained with neutral red. After locating the injection site in the TMB material, the adjacent sections were incubated with nickel/cobalt-intensified diaminobenzidine (DAB; Adams, 1981). Untreated and DAB-processed sections were mounted and stained for Nissl substance or placed in 10% formalin/PB for 5–10 days and then Nissl stained. For BDA, 50-μm-thick frozen sections were treated with Triton X-100 (0.3–0.4%), incubated in ABC Elite reagent (Vector Laboratories; Burlingame, CA), and then heavy metal-intensified as above (Adams, 1981). A 1:3 Nissl series was also prepared.

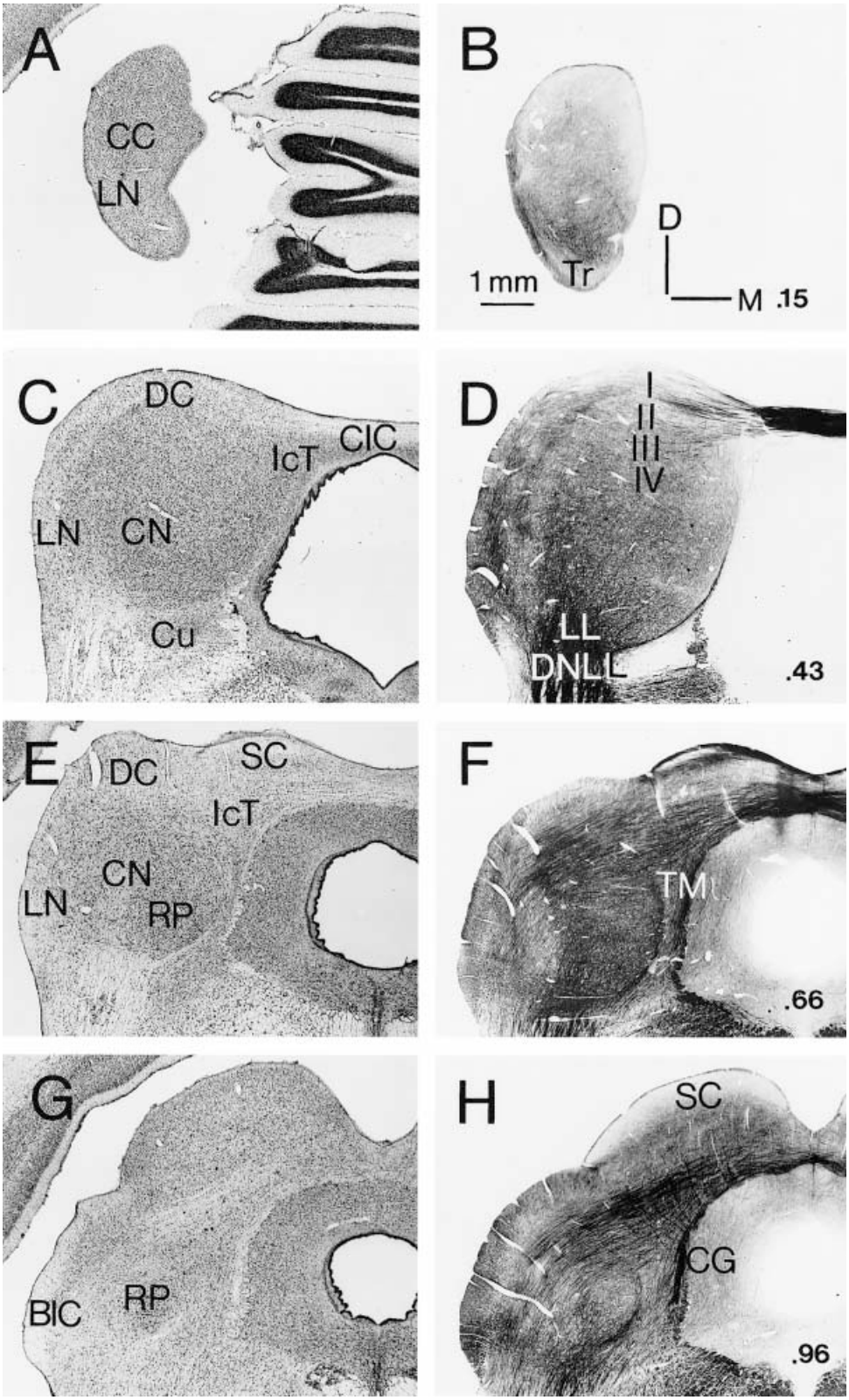
Data analysis

The anterogradely labeled axon terminals were charted on survey drawings of TMB-reacted sections. Representative sections were selected and labeled cells and axons were drawn at 125× under darkfield illumination through a drawing tube. These results were superimposed on the adjacent Nissl-stained sections, from which cytoarchitectonic subdivisions were drawn independently. DAB-reacted sections, counterstained for Nissl substance, were used to determine the boundaries of the injection sites and to identify cortical areas (Fig. 12).

RESULTS

Inferior colliculus cytoarchitectonic divisions

As an expository device, we describe briefly the architectonic scheme selected for the experimental observations.


A
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E
DC
SC
IcT
CN
LN
RP
F
TM
.66
G
BIC
RP
H
SC
CG
.96

Figure 1

This account is largely congruent with that proposed by others (Rockel and Jones, 1973a,b; Morest and Oliver, 1984; Oliver and Morest, 1984) in the cat. It or close variants of it have been used in studies of the cat (Aitkin, 1986; Beneyto et al., 1998) and rat (Faye-Lund and Osen, 1985) inferior colliculus. A corresponding series of sections immunostained for a variety of amino acid neurotransmitter candidates and Golgi-impregnated material was also used for correlative or confirmatory purposes and to examine more closely the architectonic borders for finer subdivisions of the principal nuclei.

Caudal cortex. This region was present through the caudal one-sixth of the inferior colliculus and contained many small, densely packed cells. Its neurons were distinct from the larger cells in the adjoining lateral nucleus. Many myelinated fibers passed toward the lateral nucleus as they exited the lateral lemniscal entry zone (Fig. 1B).

Dorsal cortex. This area extended from nearly the posterodorsal pole to about three-fourths the length of the inferior colliculus (Fig. 1E). Its cytoarchitecture spanned a broad range: small, scattered neurons were prevalent in the upper layer (Fig. 1C,D: I), with a progressive increase in both cell packing and somatic size (Fig. 1C) and a rich plexus of fibers in layers II–IV (Fig. 1D). In the present study, the junction between layer IV of the dorsal cortex and the central nucleus was inclined less acutely than in some previous accounts (Morest and Oliver, 1984; Oliver and Morest, 1984), resulting in a slightly expanded area for the central nucleus.

Lateral nucleus. Bounded ventrally by the sagulum and dorsally by the inferior collicular cortex, the lateral nucleus was conspicuous for its large neurons and distinctive fiber architecture. Two cytoarchitectonic regions were recognized: a medial, cell-rich part and a cell-poor lateral nucleus dominated by extrinsic axons (Fig. 1C: LN). In the most rostral quarter of the IC it was succeeded by the inferior brachium (Fig. 1G: BIC). The most distinctive features of the lateral nucleus were the large size of the neurons relative to those elsewhere in the IC and their vertical orientation. Along with the dorsal cortex, it was the principal target of CC projections. Our interpretation of its medial boundary was more expansive than in some prior reports (Oliver and Morest, 1984), chiefly at the expense of the central nucleus.

Central nucleus. This territory filled much of the central two-thirds of the inferior colliculus, and it tapered anteriorly to give rise to the rostral pole region. The neurons were heterogeneous in size and shape, and contributed to conspicuous fibrodendritic laminae oriented from ventrolateral to dorsomedial. Within this territory, there was considerable architectonic variability (Oliver and Morest, 1984), although the myeloarchitecture was uniformly heavy (Fig. 1D); from a connectional perspective it was conspicuous for the extreme paucity of corticofugal input (Figs. 2D, 13A). It was not subdivided further in the present study since no local differences in afferent input were discerned.

Rostral pole. This elongated, spherical nucleus began about two-thirds of the way through the inferior colliculus, and it was the most anterior subdivision (except for the nucleus of the brachium of the inferior colliculus). The rostral pole nucleus was distinctive in osmicated material (Fig. 1H: RP) as it displaced the central nucleus progressively (Fig. 1E). It was unclear if it had a laminar organization like that present elsewhere in the central nucleus.

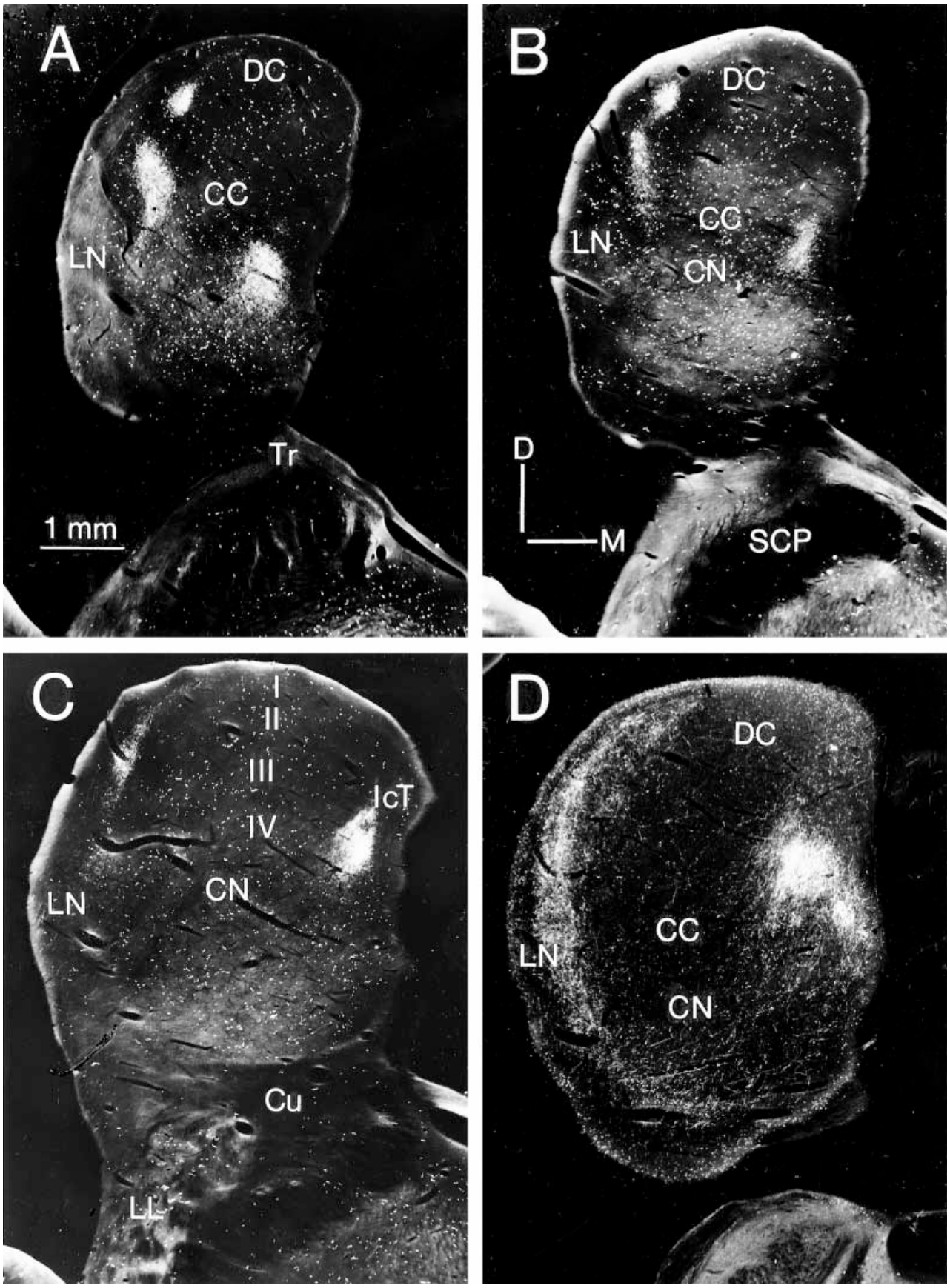
Intercollicular region. This area was a compact territory medial to layers II–III of the dorsal cortex (Fig. 1C,D) and it extended to the ventromedial border of the central nucleus (Fig. 1E). It adjoined the central gray and was present from the caudal one-fourth to about three-fourths of the length of the inferior colliculus. Commissural axons interdigitated among the neurons (Fig. 1F).

Fig. 1. Inferior colliculus cyto- and myeloarchitecture in matched pairs of sections. A,C,E,G: Nissl preparations. Planachromat, N.A. 0.04, 16.5×. B,D,F,H: Osmicated, epoxy-embedded whole mount sections. Both series are 50 μm thick. **A,B**: At 15% from the posterior tip of the inferior colliculus, the caudal cortex (CC) and the lateral nucleus (LN) were present. The caudal cortex contained mostly small neurons that were packed densely. Lateral nucleus neurons were larger and more widely dispersed by both trochlear nerve (Tr) axons en route to the surface of the brainstem and by lateral lemniscal fibers ascending toward the inferior colliculus (D:LL). **C,D**: Just caudal to the midpoint of the inferior colliculus, most of the subdivisions were present. The dorsal cortex (DC) was well differentiated. Layers I and II had fewer neurons and finer axons than the deeper layers (III, IV). The intercollicular tegmentum (IcT) comprised a mass of darkly stained cells between the commissural zone (CIC) and the underlying central nucleus (CN), which itself contained several subregions. The inferior border of the central nucleus with the cuneiform nucleus (Cu) was traversed by lateral lemniscal axons (ventrally) and fibers of the mesencephalic trigeminal nucleus (medially). The lateral nucleus (LN) had a cell rich inner half and a more fibrous external part; its medial border with the central nucleus was marked by a thin band of lateral lemniscal axons. **E,F**: The emergence of the superior colliculus (SC) and the prominence of the intercollicular tegmentum (IcT) signaled the appearance of the rostral pole (RP) nucleus. The myeloarchitecture delineated the boundary of the lateral and central nuclei. **G,H**: At the extreme rostral pole, there was labeling in only two experiments (Figs. 8, 11). At this level, only the tip of the rostral pole was present, and the brachium of the inferior colliculus (BIC) began to form as the tectofugal axons gathered laterally. The rostral pole itself was embedded in a plexus of myelinated axons. For other abbreviations, see list. Scale in panel B and orientation bar apply to all panels.

Interpretation of anterograde labeling

The WGA-HRP and the BDA experiments served independently to confirm one another (Table 1). The distribution of terminals between them was virtually identical (compare Fig. 2A–C and D). The sole exception to this was the extremely light input from areas AI and AAF throughout the central nucleus, which was revealed only by the BDA method (not shown) and consisted of just a few scattered boutons in a section. A more complete analysis is deferred to a study of the axons proper (Winer, unpublished observations). In contrast, the WGA-HRP labeling was confined entirely to the dorsomedial region of the central nucleus, at its border with layer IV of the dorsal cortex (Figs. 3D, 4D, 8F), or to the rostral pole (Fig. 11G).

At higher magnification, the BDA-filled axons formed terminal plexuses. The labeled boutons were prominent (Figs. 2D, 6). In the WGA-HRP and BDA material, fibers of passage were excluded from all plots (Figs. 3–11), and material was accepted for analysis only when the fine granular transport that denotes anterograde labeling was present. Equivocal or ambiguous observations were not included. The density of transported material in each projection was evaluated independently and qualitatively (Fig. 13A) and was largely concordant with the findings from studies using other tracers or methods (Fig. 13B).


A
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IV
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Figure 2

Corticocollicular projections

The results common to all or most experiments were that 1) the projection was heaviest in the caudalmost two-thirds of the inferior colliculus, 2) the dorsal and caudal cortices and lateral nucleus were the preferential targets of CC projections, 3) only the rostral pole of the central nucleus received an appreciable input, and 4) the principal targets were ipsilateral, although the contralateral component was usually a symmetrical subset of the former.

Area AI. The injection site was about 2 mm in diameter (Fig. 3A) with only minor diffusion into the underlying white matter (Fig. 3B: stippled), and it was remote from the border with the overlying suprasylvian fringe (SF) area and nearby AII. The pattern of medial geniculate body retrograde labeling (not shown) suggests that the injection was in the central part of AI since the transport was in the middle of the ventral division, with modest input to other thalamic auditory nuclei.

The CC labeling involved mainly the caudal cortex and the dorsal cortex, with moderate input to the lateral nucleus (Fig. 13A: AI). Terminals in the caudal cortex formed focal clusters linked by slender fingers of light labeling. The patches of heavy transport were often separated by label-poor zones up to 2 mm wide. This implies that the corticofugal projection from a single cortical architectonic field was highly divergent (since seven inferior colliculus subdivisions as well as the sagulum were labeled) or that the injection crossed areal boundaries; the latter possibility was discounted on the basis of the thalamic transport and the architectonic analysis (Fig. 12). Regions of lighter labeling abutted the focal clusters, of which the most lateral were found at the border of the caudal cortex and the lateral nucleus (Fig. 3C: CC, LN). More rostrally, three discontinuous regions of labeling were present. Terminals in the dorsal cortex formed a band ~500 μm wide concentrated in layers II and III, with foci in layer IV (Fig. 3D). These bands recalled, in both their shape and orientation, the terminal fields of cochlear nucleus axons ascending to the central nucleus (Oliver, 1984). The labeling in the central nucleus involved only the dorsomedial part. It was sparse, strictly ipsilateral, and uniformly dense along the caudorostral axis (Fig. 3D–G: CN). In BDA-labeled material, a few extremely fine CC axons with small boutons were distributed more broadly (not illustrated). More rostrally, there was an unexpectedly large input to the central nucleus near its anterior pole (Fig. 3G: CN).

Input to the lateral nucleus differed from that to the dorsal cortex in several ways. First, it was in the central part of the nucleus (Fig. 3D,E) rather than at the border. If such a pattern of input to both nuclei has some relation to characteristic frequency, this organization does not seem to be conserved connectionally. Second, the input to the lateral nucleus was a slender band ~300 μm wide with clustering in some sections (Fig. 3D) and a more continuous projection elsewhere. Although the projection involved the dorsal cortex, it had a complex suborganization, with a lateral strip of labeling at the layer I–II border (Fig. 3E: I, II) that spanned the junction between the lateral nucleus and the dorsal cortex, and a more medial input that crossed the dorsal cortex dorsoventrally (Fig. 3D).

Area AAF. In almost every respect, this experiment (Fig. 4) recapitulated the results for AI (Fig. 3). The same nuclear and bilateral distribution was evident (Figs. 3E, 4E), similar anteroposterior levels were labeled (Figs. 3C, 4C), and analogous focal and clustered distributions were present (Figs. 3D, 4D). The principal departure was a larger than expected and bilateral involvement of the central nucleus (Fig. 4D: CN) in its caudal part, a finding unique to this experiment. A further difference was that the AAF injection labeled layers II–III of the dorsal cortex most heavily, while the foci of transport from AI targeted layers III–IV. Terminals were found also in the intercollicular tegmentum (Fig. 4E).

The robustness of the labeling may reflect the increased diffusion of the injection, although the volume delivered was actually less than in the prior experiment (Table 1). Another possibility is that there are areal differences in projection density. The spatial overlap of input to specific target nuclei from different injections suggests a massive convergence of CC input (Figure 13A: AI, AAF).

Area P. These experiments (Figs. 5, 6) showed that the distribution of CC labeling was similar to that from injections in areas AI (Fig. 3) and AAF (Fig. 4). Since one case used WGA-HRP as the tracer (Fig. 5) and the other used BDA (Fig. 6), the comparability and efficacy of the two tracers could be assessed.

Each injection was centered in the rostral bank of the posterior ectosylvian gyrus, just beneath and caudal to AI (Figs. 5A, 6A). The WGA-HRP deposit diffused slightly toward, but did not reach, AI (Fig. 5B); the BDA injection was larger and it spread little (Fig. 6B). The injections did reach the depths of layer VI, although the inset (Fig. 5B) does not show this due to the curvature of the posterior ectosylvian sulcus. Since the density of the labeling was comparable to that in other regions, and the depth of the pipet track was ~2,500 μm long, the infragranular layers are likely to have been included in their entirety.

The midbrain targets of area P were similar to those of AI and AAF (Fig. 13A) with some exceptions. There was no projection to the central nucleus nor to the dorsomedial part of the dorsal cortex. In the AAF experiment, the latter labeling extended to the intercollicular tegmentum (Fig. 4E: IcT). The primary concentration of labeling from area P was in the dorsal cortex (Figs. 5E, 6E), with weaker

Fig. 2. Comparison of terminal labeling in the inferior colliculus after auditory cortex tracer injections of wheat germ agglutinin conjugated to horseradish peroxidase (A–C) or biotinylated dextran amines (D) from another experiment (see Table 1 for a complete list). In both cases the deposits involved area AI (see Fig. 12B). Caudal (A) to rostral (C) views of transport after injection of wheat germ agglutinin conjugated to horseradish peroxidase (Table 1, experiment #1324; Fig. 3). **A**: The foci of labeling were present in all inferior collicular subdivisions except the central nucleus. **B**: The same three zones had labeling. The refractile material in the central nucleus is residual erythrocytes. **C**: In the most rostral section, there is moderate transport in the lateral nucleus (LN) and more intense input to layer IV of the dorsal cortex, near the intercollicular tegmentum. **D**: Terminal labeling in the inferior colliculus after deposits of biotinylated dextran amines in areas AI and AAF (Table 1, experiment #1330). This section is at about the same level as A but appears larger since A–C were shrunken by TMB processing (see also Figs. 5 and 6). The distribution of corticollicular labeling from these areas was virtually identical (Figs. 3, 4, 13A), and the injections spanned both AI and AAF (not shown). The ensuing transport also involved the deep layers of the dorsal cortex (DC) and the lateral nucleus (LN). Lateral nucleus labeling formed a sheet ~300 μm wide that filled the dorsoventral limits of the nucleus. Planachromat, N.A. 0.04,12.5×.

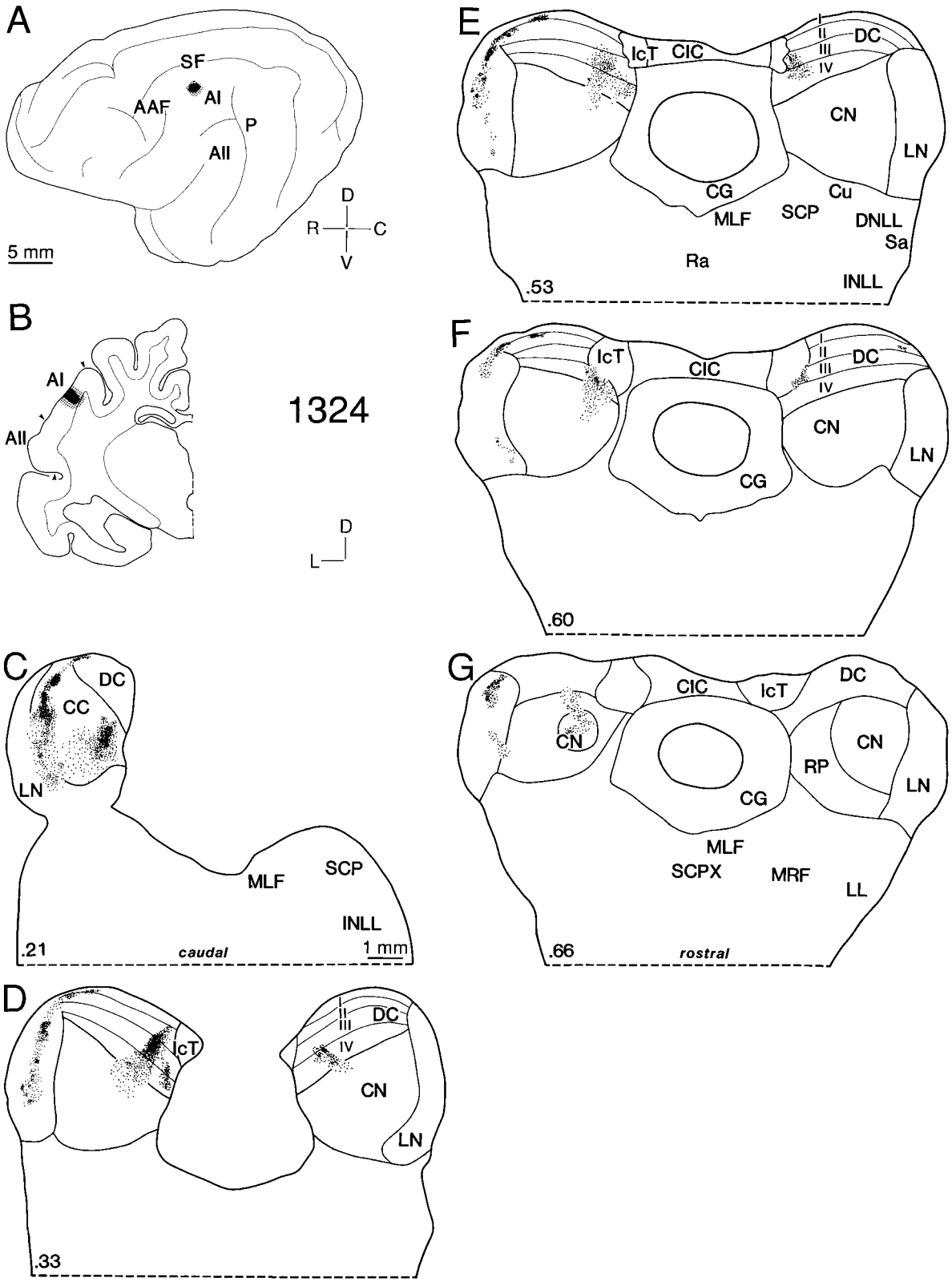

Fig. 3. Corticocollicular projection from area AI. **A**: Lateral view of reconstructed hemisphere. Solid black, center of WGA-HRP injection; stipple, diffusion of tracer. **B**: Transverse view through the center of the injection. Arrowheads, cytoarchitectonic borders. C–G: Distribution of terminal labeling (stippled) plotted from representative sections. Intervals from the caudal tip are shown as decimals in each panel (lower left), proceeding from caudal (C) to rostral (G). The major labeling was bilateral, focal, and clustered. It involved the lateral nucleus and the caudal and dorsal cortices predominantly, with little transport in the central nucleus except at its dorsomedial border. **C**: The terminal labeling virtually defined the border of the caudal cortex (CC) and the lateral nucleus (LN). **D**: There were regional foci in the lateral nucleus, whereas input to the medial part of the dorsal cortex was more homogeneous. **E**: Puffs of terminal labeling were seen in the lateral nucleus; in the dorsal cortex the input was sparser and bilateral. **F**: Discontinuities in lateral nucleus labeling were even more marked. **G**: There was a small projection to the central nucleus. Protocol for Figures 3–11: Planachromat, 15×; subdivisions derived from adjacent, Nissl-stained sections.

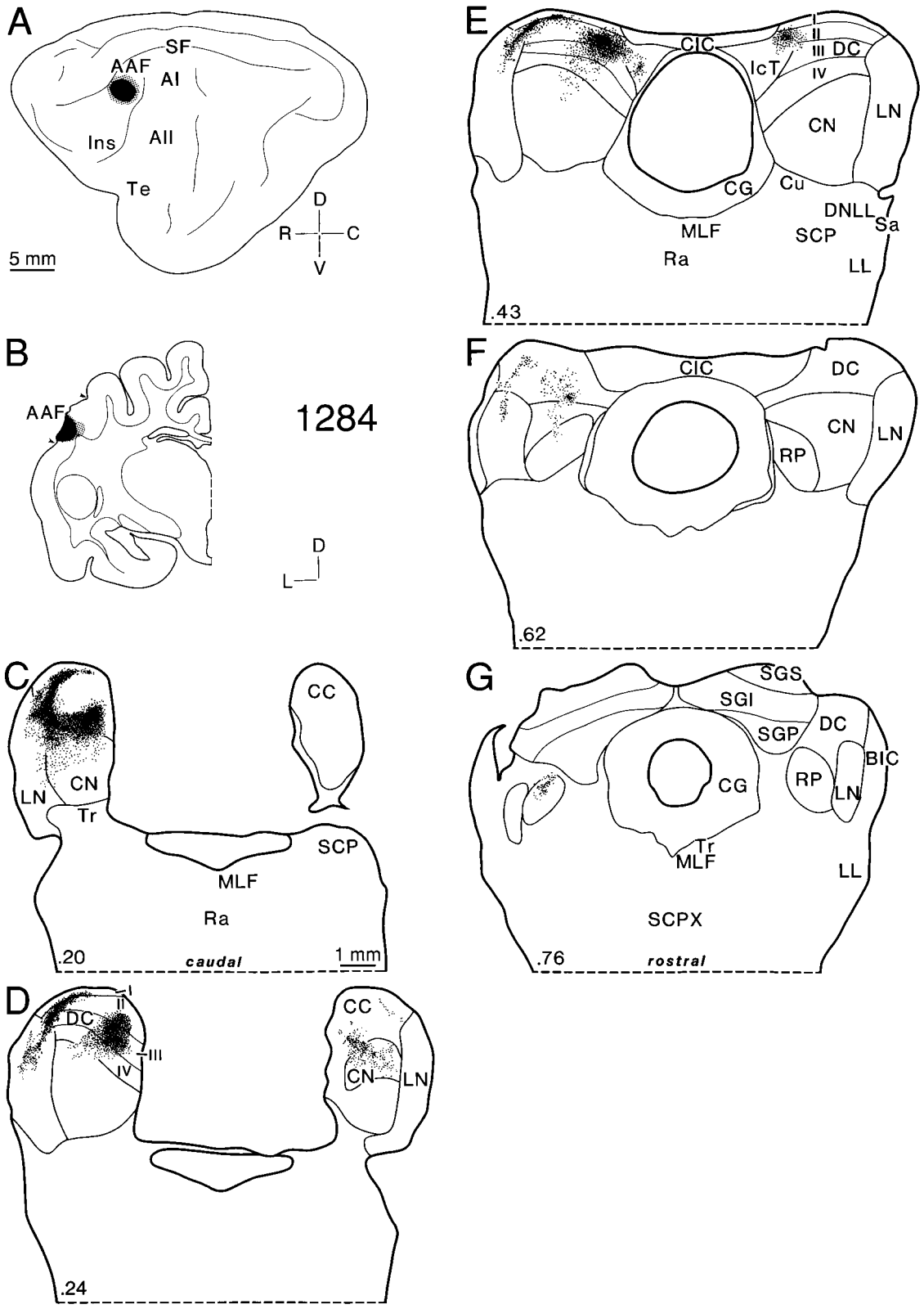

Fig. 4. Projection from area AAF. **A**: The deposit was appreciably larger, and the corresponding anterograde transport far more intense, than that from AI (Fig. 3). **B**: The injection site core did not reach the white matter, and the deposit diffused about 4 mm within AAF. The unusual sulcal pattern did not permit definitive identification of areal borders in the insular region. **C**: At this level, the caudal cortex receded as the dorsal cortex and central nucleus expanded. The labeling was robust and uniform over a large region, and often crossed nuclear borders. **D**: This section was unusual in that the contralateral central nucleus was involved at its caudal pole. Ipsilaterally, a long expanse of labeled terminals spanned the lateral nucleus and the dorsal cortex and varied in intensity. **E**: The contralateral input to the dorsal cortex and intercollicular tegmentum was again symmetrical. **F,G**: Input to the rostral midbrain was sparse, focal, and ipsilateral.

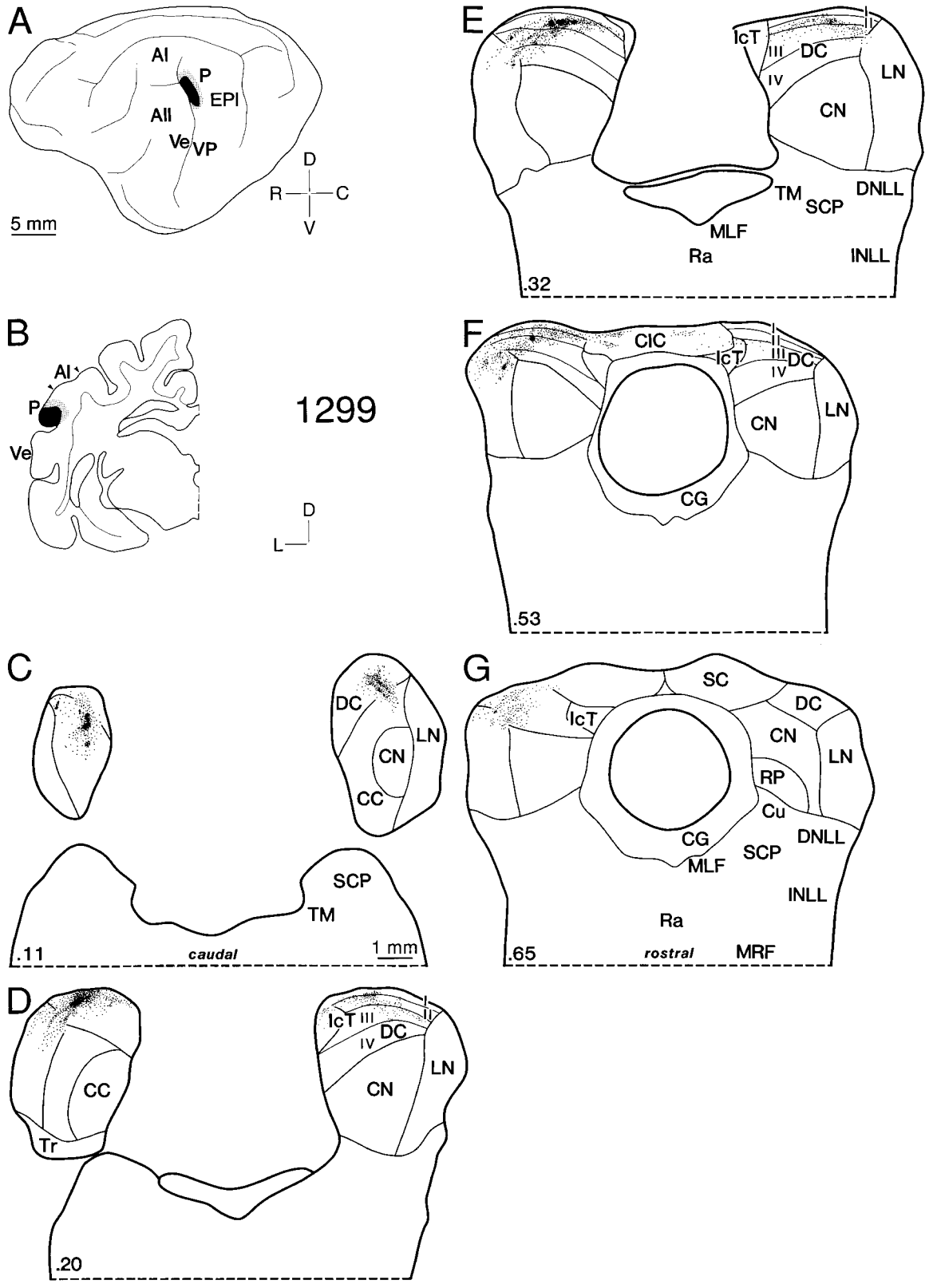

Fig. 5. Projection from area P (see also Fig. 6). **A**: The injection was ~5 mm tall. **B**: It extended deep into the caudal bank of the posterior ectosylvian sulcus; the apparent cortical thickening was an artifact of the curvature and confluence of the gyral banks, since the actual depth was <2 mm. **C**: Both ipsi- and contralateral labeling were concentrated at the junction of the dorsal and caudal cortex. **D**: The most medial parts of layers III–IV were devoid of input, bilaterally. In this and subsequent experiments, the lateral nucleus received little or no contralateral projection. **E**: There was a bilateral distribution and laminar specificity of input to the dorsal cortex. **F**: Foci of intense labeling rostral to this level were less common and occurred only after AI (Fig. 3G), EP (Fig. 8G,H) and SF (Fig. 11G) injections. **G**: The lateral part of the dorsal cortex and the dorsolateral part of the lateral nucleus received a moderate, but consistent, input.

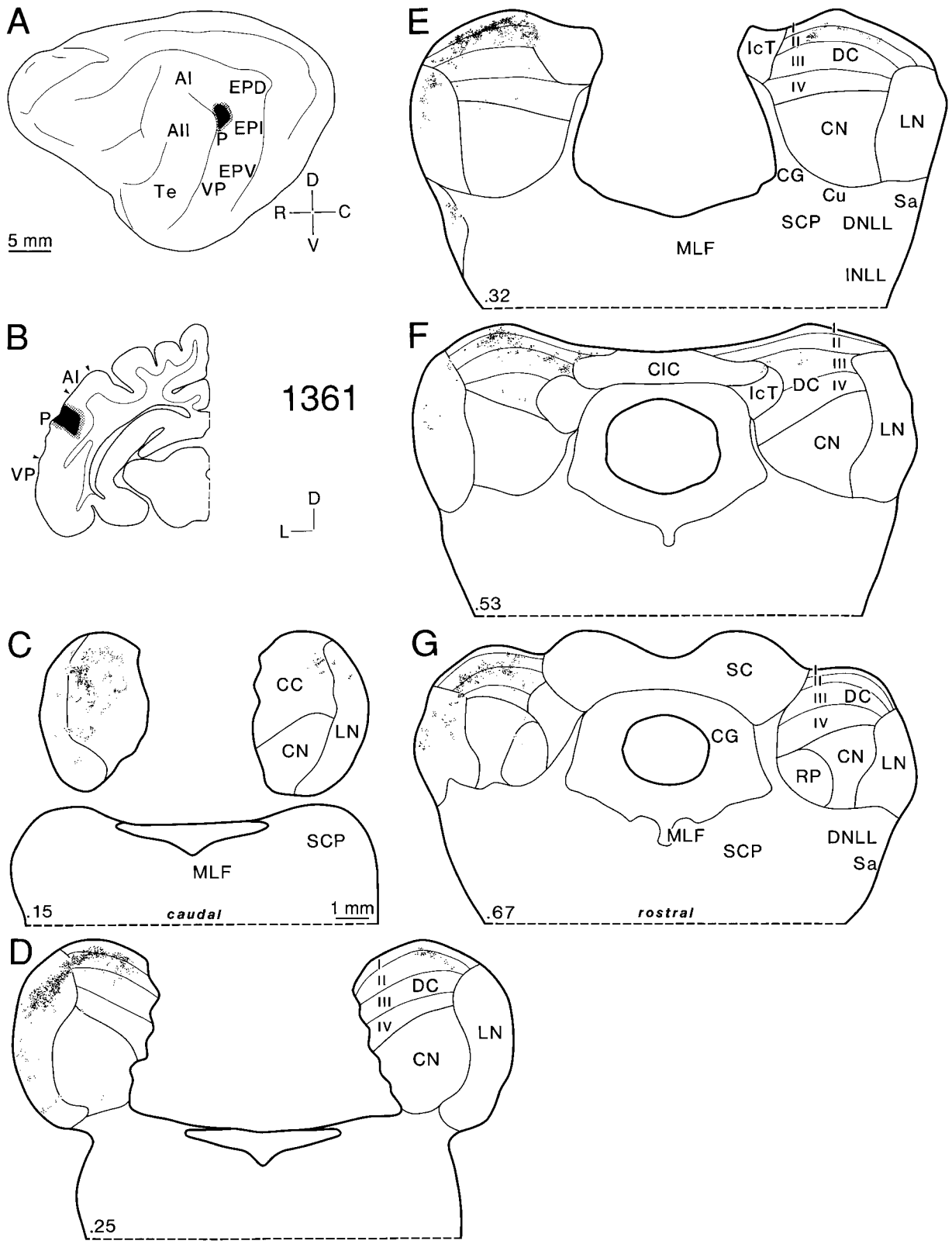

Fig. 6. Projection from area P studied with BDA. **A**: The locus of injection (and the sulcal pattern) closely matched the WGA-HRP deposit in area P (Fig. 5). **B**: The gyral distortions and the actual cortical depth resembled those in Figure 5B. **C**: This tracer often revealed fine or minute projections (compare Figs. 5C and 6C:LN [right side] or Figs. 5D–G and 6D–G [left side], where BDA labeled a few central nucleus boutons that were absent in the WGA-HRP experiments). These were not sufficient to constitute even a light projection (Fig. 13A). **D**: There was involvement of layers I and III. **E**: The dorsal and central part of the lateral nucleus was labeled, whereas AII deposits targeted the most lateral part (Fig. 7C–E). The input to a nucleus was sometimes area specific. Three tonotopically arranged fields (AI [Fig. 3D], AAF [Fig. 4D], and P [Fig. 6D,E]) projected here, as did AII, which is devoid of tonotopy (Schreiner and Cynader, 1984). **F**: The BDA experiments readily resolved terminal clusters 100–300 μm in diameter; since the injections saturated a cortical expanse ~4 mm long, these clusters may reflect the contribution of several cortical modules to the midbrain as well as the superior resolution of this tracer. **G**: The BDA experiments revealed fundamentally similar, though slightly more extensive, projections than those in the corresponding WGA-HRP studies (see Fig. 5G).

input to the caudal cortex (Figs. 5C, 6C) and the lateral nucleus (Figs. 5F, 6D). As in the prior experiments, the projection to the dorsal cortex was lamina-specific, involving layer II principally and, to a lesser degree, layer III; likewise, it was bilateral and there were regions of clustered, focal input (Fig. 6E) as well as more diffusely organized terminal fields (Fig. 6G). In the BDA experiment, the projection to the sagulum was plotted to document the sensitivity of the tracer (Fig. 6E); these data were not included in every experiment (Figs. 3–5, 7) since they are the subject of a separate study (Beneyto et al., 1998).

Area VP. In two experiments (one using WGA-HRP, the other BDA) the cortex along the caudal bank of the posterior ectosylvian sulcus ventral to area P (not shown) was injected. The distribution of midbrain labeling in these experiments closely resembled the patterns seen from areas AI (Fig. 3), AAF (Fig. 4), and P (Figs. 5, 6). The principal projections were to the intermediate layers of the dorsal cortex, and to the caudal cortex and intercollicular tegmentum (Fig. 13A); the latter projection was the strongest input to this region from a primary field. The labeling in the lateral nucleus was lighter than that of other tonotopic areas (Fig. 13A).

Area Ve. These deposits of WGA-HRP in a single experiment were in the rostral bank of the posterior ectosylvian gyrus, just beneath the caudal part of AI (not shown). As in the area AI and AAF experiments, the distribution of CC labeling was strongest in the caudal collicular cortex, with additional input to the dorsal cortex (Fig. 13A). Just as in the experiments involving areas P and VP, the central nucleus received no projection. In other respects the experiment resembled those with deposits in tonotopic areas.

Area AII. Because of a gradual increase in cortical thickness along the crest of the sylvian gyrus and the slightly oblique angle of the track, this injection did not reach the white matter in every section (compare Figs. 7B and 12C). The retrograde transport in the medial geniculate body (not shown) involved chiefly the dorsal division nuclei with comparatively little labeling in the ventral division, a pattern consistent with an AII injection (Winer et al., 1977).

As in the prior experiments (Figs. 3–6), the CC projection was bilateral, favored the ipsilateral side, and involved nuclei outside the central nucleus. Once again, the main targets were the caudal cortex, the dorsal cortex, and the lateral nucleus; there was also significant input to the intercollicular tegmentum. On the whole, these projections were slightly less extensive and lighter than those for area VP (Fig. 13A). There were only a few of the clusters of dense terminal labeling characteristic of AI (Fig. 3) or field P (Fig. 5) injections. These foci were clearest in layer I of the dorsal cortex (Fig. 7F) and in more rostral parts of this region (Fig. 7G). The moderate layer I involvement was common only to areas AII, posterior ectosylvian, and temporal cortex (Fig. 13A).

Projections to the caudal cortex (Fig. 7C: CC) and lateral nucleus (Fig. 7D: LN) were moderate in density and almost devoid of clustering. However, they were as restricted as those in the other cases. Another salient feature was that, whereas the nuclear targets were much like those in the prior experiments, the local distribution was distinct. In particular, input to the caudal cortex terminated in the dorsolateral and most superficial parts (Fig. 7C) rather than more centrally as in prior experiments (Figs. 3C, 4C). The same was true of the projection to the lateral nucleus, which ended in the most external part (Fig. 7C–G), unlike that from areas AI (Fig. 3D) or AAF (Fig. 4D), which terminated more medially.

Unique projection targets included the intercollicular tegmentum, which received both focal and widespread input (Fig. 7F: IcT). The projection pattern appears to be part of a widely dispersed band of terminals that defined much of the perimeter of the inferior colliculus, from the lateral nucleus to the superficial dorsal cortex to the intercollicular tegmentum. Such divergence is a hallmark of the CC pathway (Fig. 13A). There was a minor, but consistent, ipsilateral projection to the intermediate and deep layers of the superior colliculus (Fig. 7H: SGI, SGP).

Area EPI. This (Fig. 8) and the insular cortex experiment (Fig. 9) differed somewhat from the prior cases in their CC projections, with respect to both the nature of the targets and the intensity of the labeling. This projection was widespread, involving every inferior colliculus nucleus except the rostral pole. Unlike most of the other cases, the labeling was concentrated rostrally and was almost entirely ipsilateral. The most noteworthy feature was the broad input to the rostral central nucleus.

The injection site was ~4 mm long and 3 mm tall (Fig. 8A); it was among the largest in this series, and it encroached slightly into the white matter of the posterior ectosylvian gyrus. The tracer may have spread caudally to involve perivisual cortex (Bowman and Olson, 1988a,b). The inferior colliculus targets included every part except the rostral pole nucleus. The EPI projection was lighter than many of the other CC inputs (Figs. 4, 10), especially caudally, and the labeling involved larger areas in single nuclei than in other cases (compare Figs. 3F and 8F). Rostrally, there was a surprisingly large projection to the ipsilateral central nucleus (Fig. 8G,H). Terminal fields were diffuse, with few of the regions of intense labeling so marked in other experiments. A second feature was that the bulk of the labeling terminated in more rostral inferior collicular territories, whereas in each of the prior experiments most input was in the caudal inferior colliculus. This suggests a disjunction between more caudal, auditory dominated, and rostral, polysensory affiliated, collicular territories. The labeling in the dorsal cortex of the anterior part of the inferior colliculus (Fig. 8G) and in the deep layers of the superior colliculus (Fig. 8H) was unusually robust and supports this idea. However, the involvement of the visual belt cortex calls into question the possible auditory cortical origin of the projection to the superior colliculus. Finally, the spatial continuity of terminal labeling across nuclear boundaries was conserved here, much as in prior experiments.

Given the complex functional affiliations of this region, it is not entirely surprising how light the CC input was (Fig. 13A). This contrasted with the massive corticothalamic projection to both auditory and nonauditory nuclei (not shown), a pattern consistent with the areal designation of the injection site. Despite the overall low density of the CC input, both the divergence of the projection in terms of its nuclear targets (Fig. 13A) and the anteroposterior limits of the transport–which involved 80% of the length of the inferior colliculus–were the largest in the series. Thus, eight of nine possible inferior collicular nuclei received input, as did all three extracollicular

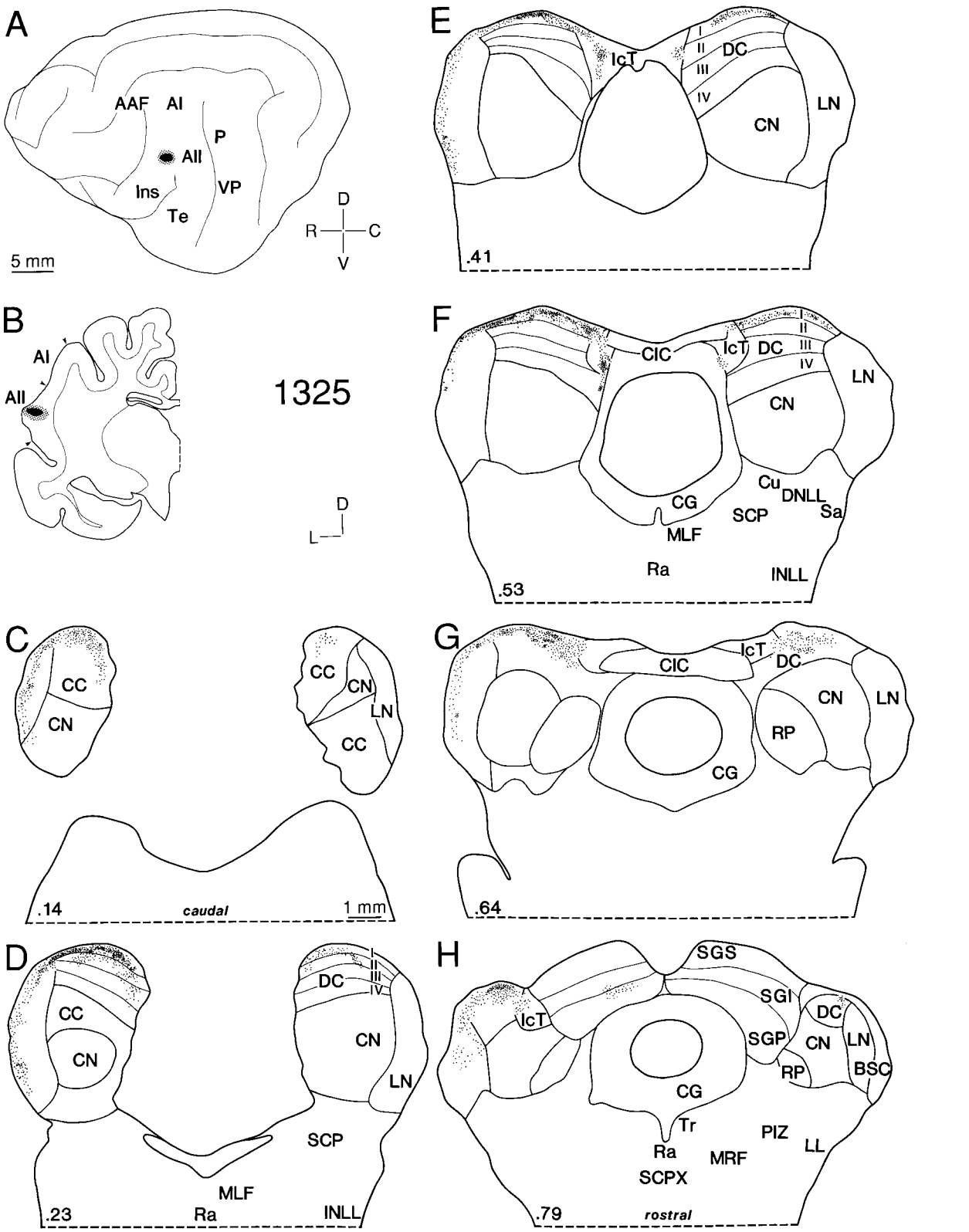

Fig. 7. Projection from area AII studied with WGA-HRP. **A**: The deposit was in central AII and highly circumscribed. **B**: The injection involved all of layer V and only the most superficial part of layer VI; caudally, layer VI was saturated. **C**: Ipsilateral labeling ringed the dorsal and lateralmost parts of the inferior colliculus. **D**: Most of the transport was concentrated in the most superficial parts of the lateral nucleus and layer I. **E**: There was substantial involvement of the intercollicular tegmentum along its length. **F**: The contralateral projection matched the ipsilateral input except in the lateral nucleus. **G**: Changes in the concentration of lateral nucleus labeling along its caudorostral extent suggested segregation of input (compare Fig. 7E–G). **H**: A light (but variable) projection to the superior colliculus aligned AII with two other nontonotopic fields (Fig. 13A).

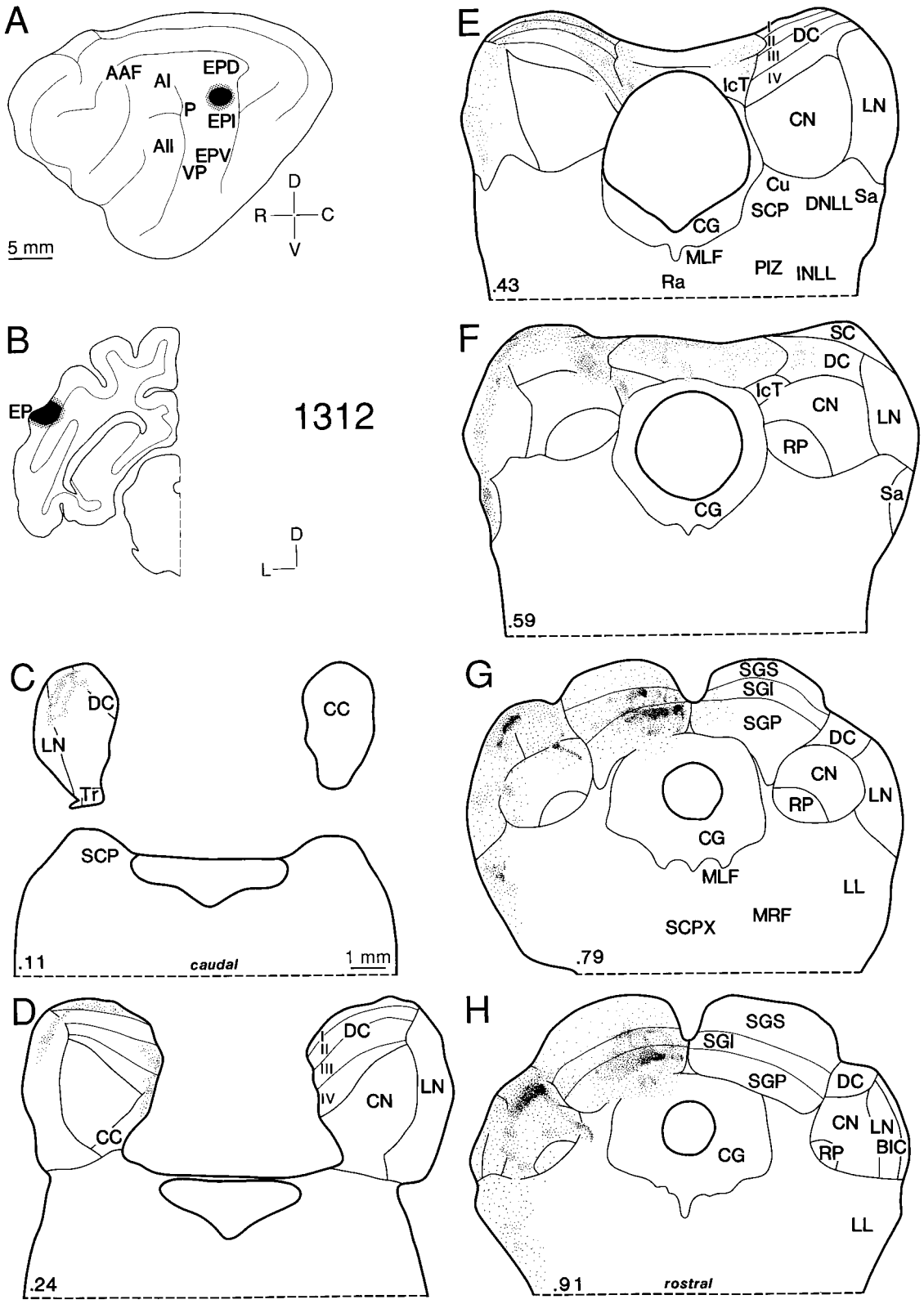
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Figure 8

targets. Such connectional divergence was consistent with a polymodal affiliation.

Area EPD. The projection pattern from area EPD (not shown) was virtually identical to that from EPI (Fig. 13A). It differed from the latter only in the placement of the deposits, which were at the crest of the posterior ectosylvian gyrus, just behind area AI. This injection did not involve perivisual cortex.

Area Ins. Deposits in the insular cortex (Fig. 9) produced a pattern of midbrain labeling that was unique since it involved the cuneiform nucleus in the subcollicular tegmentum and the central gray more extensively than any other case. The injections were centered in the anteroventral bank of the pseudosylvian sulcus (Fig. 9A), and they encroached slightly into the underlying claustrocortex (Fig. 9B). Unlike every other experiment, in this case there was no labeling in the lateral nucleus and very little in the dorsal cortex (Fig. 13A: Ins), nor was the caudal cortex involved. The caudalmost section had a focus of moderately heavy labeling in the subcollicular tegmentum that extended slightly into the lateral nucleus (Fig. 9C: LN). In the next section the labeling formed three independent masses: one was in the cuneiform nucleus proper, along its dorsal half (Fig. 9D: Cu), a second was in the caudal part of the central gray (Fig. 9D: CG), and the last target was the sagulum (Fig. 9D: Sa). In subsequent sections even more nuclei were involved as the intercollicular tegmentum declined in size and a substantial and bilateral input to the central gray (Fig. 9E: CG) as well as a far finer projection to the most superficial part of layer I in the dorsal cortex (Fig. 9E: I) emerged. Near the rostral pole, where the dorsal cortical layers were no longer distinguished, the CC input to the medial part of the dorsal cortex was larger (Fig. 9F: DC). The projection to the central gray was conserved in subsequent sections, although it was smaller and more concentrated, and a modest input to the medial part of the deep layers of the superior colliculus was present in a few sections (Fig. 9G: SGP). The labeling in the dorsal cortex grew progressively in rostral sections, and smaller foci of labeling were present in and about the peribrachial region.

Area Te. This experiment (Fig. 10) embodied parallels with the other cases and some unique features. For example, it had the ring-like and bilateral projections that defined most of the other fields. Despite the locus of injection in polymodal auditory association cortex, there was no or only a minute projection to the superior colliculus. Although the case is nearly as divergent from an areal perspective as the EP experiment (Fig. 8), almost all the terminal labeling was moderate or heavier than in the latter cases (Fig. 13A).

The injection was ~5 mm in diameter, the largest in this account, and it filled the cortical convexity between the posterior ectosylvian and pseudosylvian sulci (Fig. 10A). The deposit involved much of the temporal field, although some parts of it did not reach layer VI (Fig. 10B).

As in prior experiments, the lateral nucleus and caudal cortex were labeled, the latter receiving both a dense and a broadly distributed input. Likewise, every layer of the dorsal cortex was labeled, especially in its most medial part. A noteworthy feature was that the layer I projection was confined to a narrow band in the most superficial dorsal cortex (Fig. 10D–F). Input to layers II–IV (Fig. 10D) was wider than that from AII (Fig. 7E) or EPI (Fig. 8D). The strongest projection, to the intercollicular tegmentum (Fig. 10E: IcT), filled much of this nucleus and then ceased abruptly (Fig. 10E,F) as the axons crossed the nuclear border and ended bilaterally in the central gray. The largest contralateral descending projection from the temporal lobe was a modest input to the intercollicular tegmentum (Fig. 10F). As in nearly all of the experiments (Figs. 3–7), most of the labeling was concentrated in the caudal half of the inferior colliculus (Fig. 10C–F). Areas Te and AII shared many CC targets (Fig. 13A).

Area SF. To inject the suprasylvian fringe (SF) cortex (Fig. 11), the overlying middle suprasylvian gyrus was retracted above area AI. The four deposits spanned the caudorostral limits of SF with little or no involvement of AI or AAF (as denoted by the absence of labeling in the ventral division of the medial geniculate body [not shown]). There was marginal encroachment of the deposit into the visual association cortex (Figs. 11B, 12B).

As in many of the preceding experiments, the CC labeling was bilateral, strongest ipsilaterally, approximately symmetrical, and involved every inferior colliculus subdivision except the caudal part of the central nucleus and the dorsal cortex. The heaviest input was to the ipsilateral intercollicular tegmentum, which was virtually defined by this projection (Fig. 11D: IcT); the contralateral IcT labeling was in the lateralmost part of the nucleus. The lateral nucleus (Fig. 11D,E: LN) projection was confined to a sheet that spanned the dorsoventral axis centrally. The rostral pole (Fig. 11F: RP) received a moderate, bilateral projection whose extent suggested that the SF deposits were subtotal (even though they were the largest in volume in the WGA-HRP series; Table 1), or that a projection from some other, unknown cortical area would fill the unlabeled part, or that it was devoid of input. Two other projections, both extracollicular, were present. The deep layer of the superior colliculus, especially its intermediate part, was filled either with puffs (Fig. 11F: SGP) or a

Fig. 8. Projection from area EPI. **A**: This injection was near the border between the intermediate and dorsal parts of the posterior ectosylvian gyrus. **B**: The deposit filled much of EPI and spread slightly into the immediately subjacent white matter. No architectonic boundaries are shown since adequate grounds for subdividing this area are not yet available. Caudally, the deposits encroached onto the perivisual cortex (Bowman and Olson, 1988a,b). **C**: In this and subsequent panels, the inferior collicular labeling was the lightest in any experiment (Fig. 13A), yet it had among the greatest caudorostral distribution (from 11 to 91%; see Fig. 11G). **D**: The projection to the lateral nucleus involved the central part primarily. The labeling in layers III and IV was on their medial margin in this and subsequent sections. **E**: The input to the intercollicular tegmentum was light and bilaterally symmetrical. All dorsal cortex layers were involved to some degree: labeling extended mediolaterally throughout layers I and II and was more limited in layers III and IV. **F**: The entire perimeter of the inferior colliculus and the nuclei adjoining it ventrally (the sagulum) and medially (the commissural zone) received light transport. **G**: The modest labeling in the lateral nucleus/dorsal cortex was succeeded more rostrally by small but intense foci of transport, which extended well into the ipsilateral central nucleus. The ventral half of the superior colliculus was involved extensively along its mediolateral extent, suggesting that the central visual field was represented preferentially (compare with Fig. 11H). **H**: Labeling was even more complex and widespread. It ranged from sparse and diffuse (in the lateral lemniscus) to intense and focal (dorsal cortex). The widespread input to the rostral central nucleus was unique in this experiment. All parts of the inferior colliculus at this level were involved, as was the dorsolateral part of the central gray and the subcollicular tegmentum. The latter projections were ipsilateral.

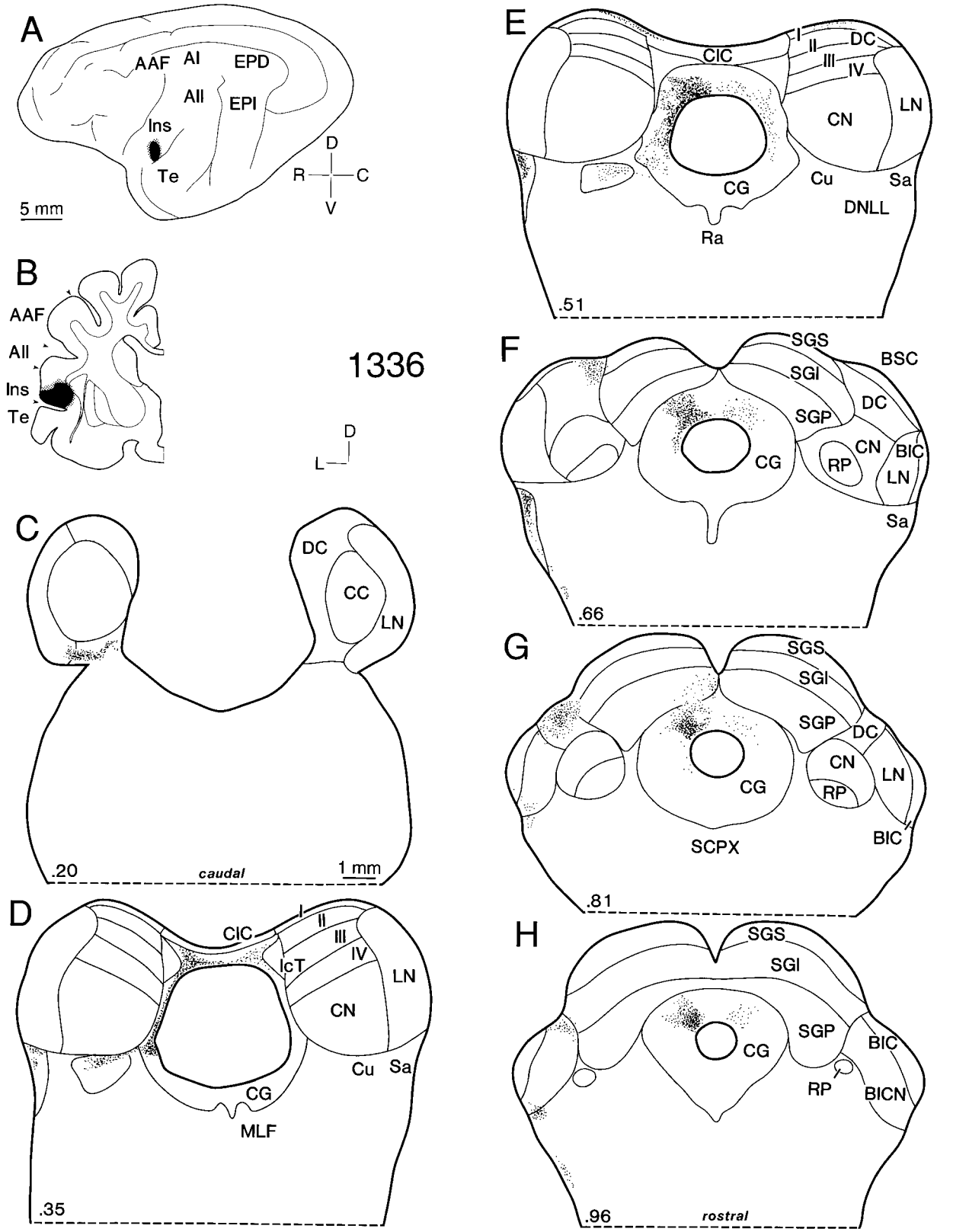

Fig. 9. Projection from area Ins. **A**: The deposit was confined to insular cortex and abutted the pseudosylvian sulcus. **B**: The cortex along the dorsal bank of the pseudosylvian sulcus was saturated with tracer, with minor involvement of the claustrocortical white matter. **C**: The most caudal labeling was in the subcollicular region that, more rostrally, will constitute the cuneiform nucleus. **D**: Input to the cuneiform nucleus (Cu) was confined to the dorsal half. Labeling in the caudal central gray (CG) differed from other targets in that its bilateral projection was only partially symmetrical. **E**: The central gray labeling was robust and included both focal and diffuse projections. Input to the cuneiform nucleus and sagulum was still present, but the rostral intercollicular tegmentum was devoid of labeling. **F**: The dorsal cortex received a substantial projection near the superior colliculus border. The central gray labeling was now focal, symmetrical, and progressively restricted. Scattered peribrachial labeling was present as well. **G**: The medial part of the deep superior collicular gray (SGP) received weak input, and the rostral pole of the dorsal cortex was nearly filled. **H**: Projections to the peribrachial tegmentum formed small puffs, and the CC input to the central gray persisted well past the rostral pole of the inferior colliculus.

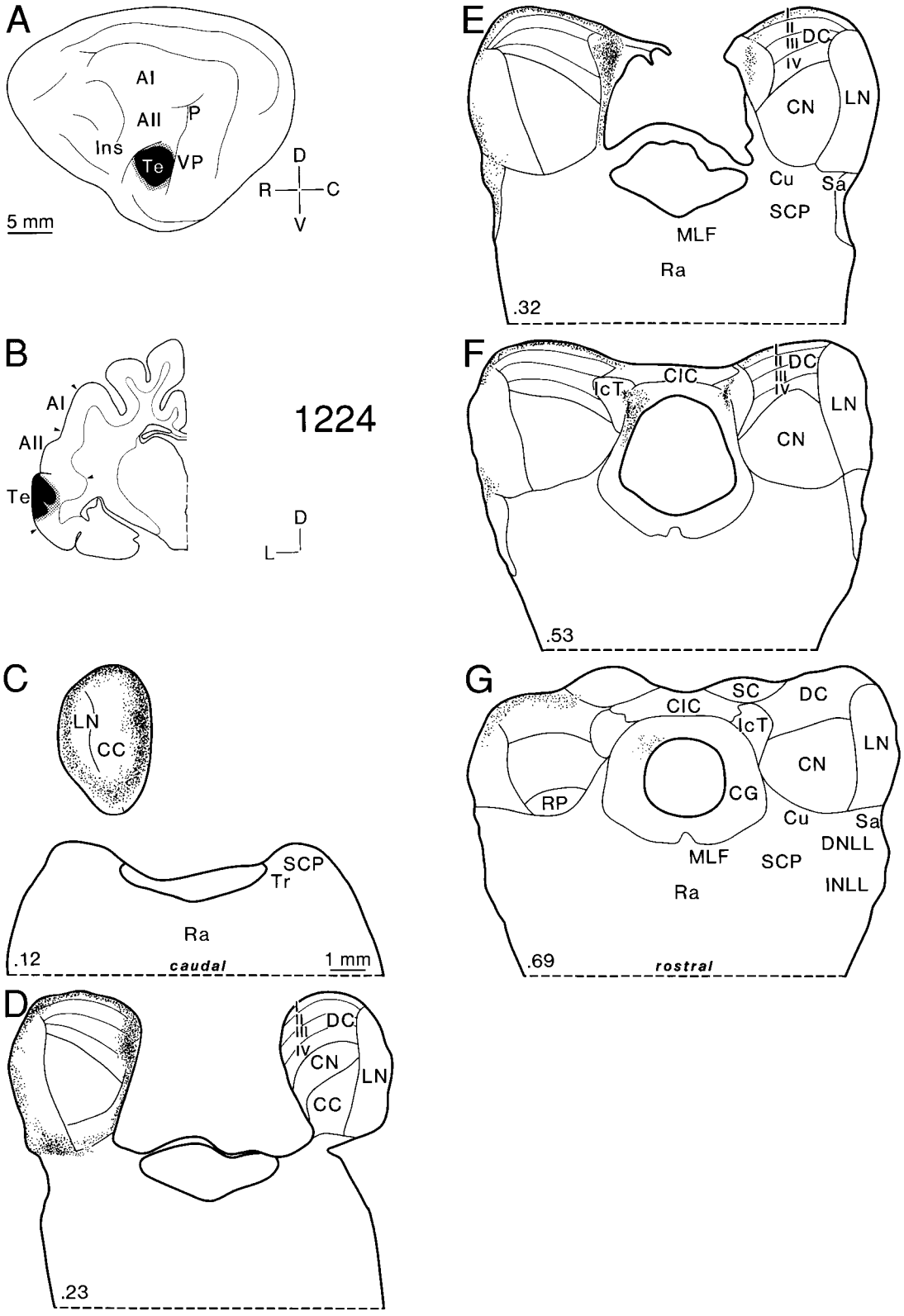

Fig. 10. Projection from area Te. **A**: The deposit was among the largest in the study. **B**: Tracer filled much of the temporal field and the tracer diffused to the white matter border. **C**: The labeling ringed the inferior colliculus caudally (C–E). The projection to the lateral nucleus and the caudal cortex was widespread and uniformly dense. **D**: The superficial half of layer I received a substantial projection, and the deep layers of the dorsal cortex had input across their long axis. Labeling intensity was nucleus specific and not level specific; there was an abrupt change at the ventral border of the dorsal cortex and the caudal cortex. Although the labeling decreased rostrally, target identity seemed more critical than anteroposterior locus as an index of input strength. **E**: Projections were bilateral and symmetrical except those to the sagulum and subcollicular region. The intercollicular tegmentum received especially dense input. Labeling was distributed around the perimeter and the projection to the lateral nucleus diminished progressively. **F**: The input differed in each nucleus, with light input to the central gray and decreased contralateral labeling. **G**: The projection to layer I of the dorsal cortex was conserved through the caudorostral series. It was smaller but more focal than that from EPI (Fig. 8H).

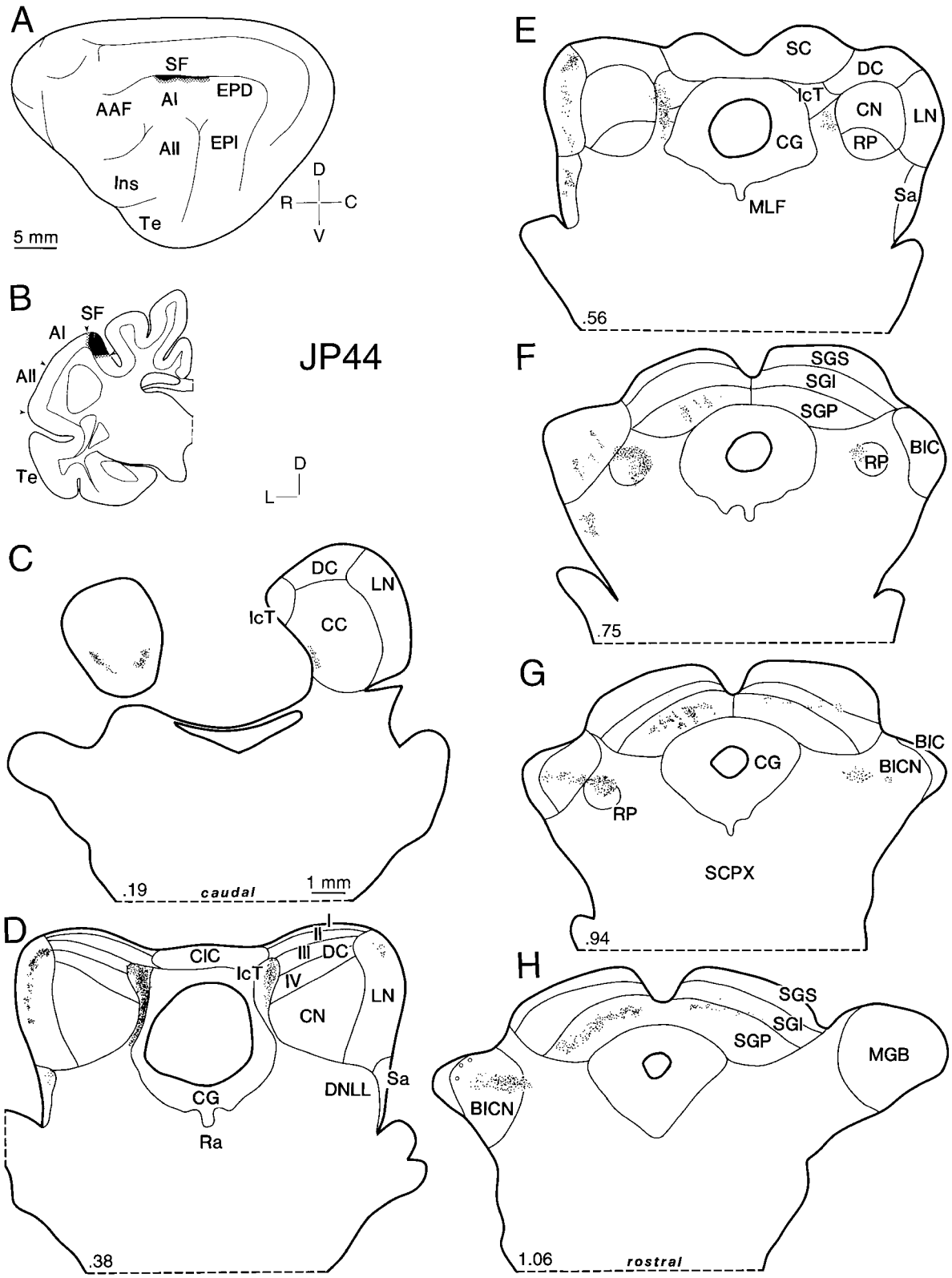
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Figure 11

continuous band of labeling (Fig. 11H). This could reflect the proximity of the injections to visual association cortex. Since the anterior and posterior lateral suprasylvian visual areas were involved (Fig. 12B,C: ALLS, PLLS), the question of a superior colliculus projection remains open. The brachium of the inferior colliculus (Fig. 11G: BIC) contained a mediolateral strip of input, and its bed nucleus had a few retrogradely labeled neurons (Fig. 11H: open circles).

DISCUSSION

Specificity and topography of corticocollicular projection

The primary finding in the present study is that all 11 auditory cortical areas project to the inferior colliculus. This suggests that the auditory cortex as a whole might exert a more widespread and perhaps a more powerful effect on the auditory midbrain than prior work concluded on the basis of studies of projections from fewer areas (Andersen et al., 1980b) or from using methods superseded by more sensitive tracers (Diamond et al., 1969). Our results extend the limits of connectionally defined auditory cortex as determined by corticocollicular projections to include association areas like the insular (Clascá et al., 1997) and temporal (Sindberg and Thompson, 1962) fields, regions whose affiliations with the auditory system were less apparent than they now are. We conclude that nonprimary areas must therefore have considerable influence on inferior collicular operations, and perhaps even a more extensive and divergent role than the primary areas (Fig. 13A).

A second conclusion is that the labeling from every experiment had a limited distribution in the inferior colliculus. This outcome is not unexpected with regard to the tonotopic fields such as AI or AAF (Reale and Imig, 1980), whose connections with the auditory thalamus have a topographic, point-to-point precision (Brandner and Redies, 1990). It is, however, surprising to find that cortical areas apparently devoid of any systematic representation of characteristic frequency had a pattern of CC input as ordered and focal as their tonotopically arranged counterparts. This point has been made before, with regard to AII (Andersen et al., 1980b). It supports the idea that tonotopy (not to mention other such topographic entities) may not be the most appropriate conceptual or functional metric for thinking about how the cortex is organized (Weinberg, 1997) and how it influences subcortical nuclei. Comparing projections from a tonotopic area, AI (Fig. 3) with those from area Te (temporal cortex; Fig. 10), a field without tonotopy and whose affiliations are polymodal (Sindberg and Thompson, 1962; Winer, 1992), is illuminating. Although the projections from each area differ, they nonetheless share many targets (Fig. 13) and are comparable in overall density. Both the cytoarchitecture of these cortical areas and their thalamocortical and corticothalamic projections are consistent with their territorial designations.

The present injections are sufficiently small to suggest that the total CC projection is substantial. If the unlabeled regions near labeled zones in the same inferior colliculus subdivision receive projections from uninjected cortical areas, then the CC system could be a mosaic in which corticofugal projections from different areas interdigitate and overlap. The strongest evidence for this position is the powerful divergence of almost every area's CC projection: of nine possible projections from each area to specific midbrain nuclei, up to eight occurred (Fig. 13A). If subregions of the same (or of different) areas converge onto an inferior colliculus locus, the individual projections then might act as "and" gates to facilitate or check collicular output. Data supporting such convergent specificity is the light but consistent input to layer I in the dorsal cortex from nearly all cortical areas injected (Fig. 13A). An argument against the specificity of layer I input is that it is a subset of the larger projection to the dorsal cortex as a whole. Three lines of evidence support the interpretation that this projection is specific. First, the input to layer I, though usually light, ranged from sparse to medium, suggesting that the projection differed across areas. Second, the input to subjacent layers of the dorsal cortex was likewise variable and specific for each cortical field. Third, the range in the strength of this projection was confirmed with another tracer in different experiments.

As a rule, the projections from tonotopic areas were by far the strongest in the dorsal cortex. How such overlapping input from tonotopic and nontonotopic cortical areas might be arranged is a question that could require a double-labeling strategy in which different anterograde tracers are injected in various cortical areas and their terminal patterns compared. Such a strategy has been used to explain how the construction of combination sensitivity in the auditory thalamus may result from the convergence of different inputs (Wenstrup and Grose, 1995 [mustached bat]). Failure to find such overlap would naturally have different implications for the distribution of CC influence.

There are strong parallels in collicular projection patterns from many cortical areas. They involve the dorsal cortex, lateral nucleus, and intercollicular tegmentum, all

Fig. 11. Projection from area SF. **A**: The deposits formed a row along the crest of the posterior ectosylvian gyrus and extended to the posterior ectosylvian (EP) border, whereas its rostralmost part did not enter the anterior auditory field (AAF). **B**: The deposits filled the suprasylvian fringe area without invading AI; there was probably incursion into the lateral part of the lateral suprasylvian area (Fig. 12B:ALLS). Tracer diffusion was <1 mm mediolaterally and the four deposits formed a confluent line. **C**: The plane of section was asymmetric and dorsal structures were more rostral than usual. In the ipsilateral caudal cortex (CC), two mirror image puffs of transport occurred, with only one contralaterally. **D**: In the lateral nucleus (LN) the main ipsilateral input was in the central part. The transport to the ipsilateral intercollicular tegmentum (IcT) filled it completely, and the contralateral projection labeled its lateral half. **E**: Small foci of input to the ipsilateral central nucleus could represent terminal fragments bordering the intercollicular tegmentum (IcT) or the most caudal labeling extending from the rostral pole. The dorsal position of the transport favors the former idea, though the ventral limits of the intercollicular zone are obscure. **F**: A complex projection pattern emerged rostrally, with labeling in the superior colliculus (SC), sagulum (Sa), and rostral pole (RP); the nucleus of the brachium of the inferior colliculus (BICN) received sparse to moderate input. **G**: The projections were moderate in density and were distributed widely and asymmetrically. They involved the ipsilateral deep (SGP) and contralateral intermediate (SGI) layers of the superior colliculus, the brachium of the inferior colliculus (BIC) and its nucleus (BICN), and the rostral pole of the inferior colliculus (RP). **H**: This was among the most rostral midbrain sections in any experiment with significant labeling. The input to the deep superior colliculus spanned the central part of the deep gray.

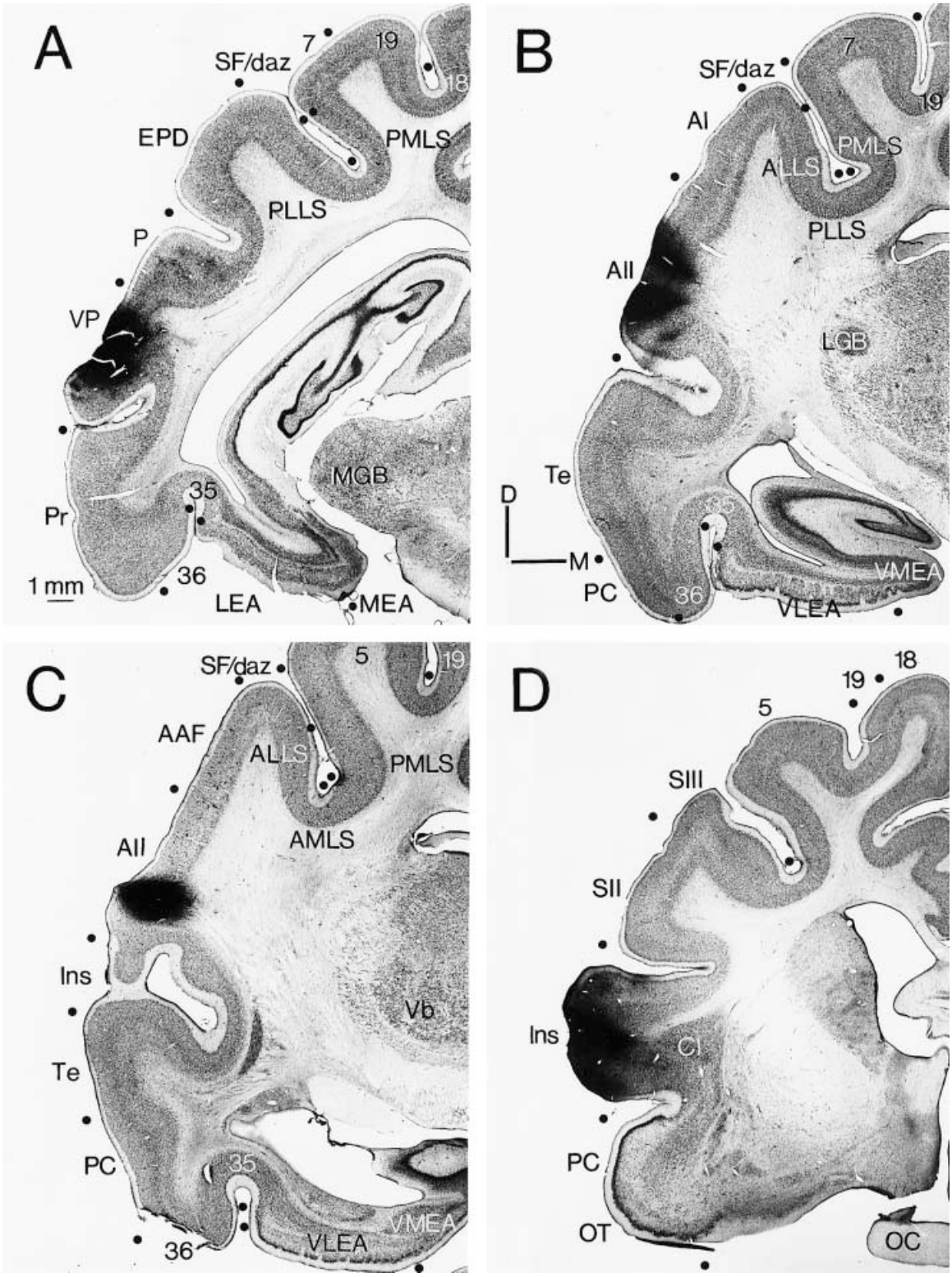

Fig. 12. Cortical cytoarchitecture and representative deposit sites. The visually affiliated areas were identified using the architectonic criteria described in combined electrophysiological-histological studies (Tusa et al., 1981). The limbic and perihippocampal fields were related to subdivisions in architectonic and connectional investigations (Witter et al., 1989). **A**: The posterior ectosylvian gyrus abutted the perivisual cortex (dorsally) and the caudal perilimbic areas (ventrally). Thickening of area VP was the result of the gyral curvature and the beginning of the posterior ectosylvian sulcus. BDA deposits, experiment #1358 (Table 1). Planachromat, 1×, macro lens. **B**: Several auditory fields were present at the rostral pole of the lateral geniculate body. AI had a highly granular layer IV and a conspicuously light layer Va, while in AII and SF/daz large pyramidal cells were present in the infragranular layers. BDA deposits, experiment #1383. **C**: The insular area was thinner than AII, and had a less developed layer IV and a more variable cytoarchitecture. Temporal cortex (Te) had a robust layer III and a layer Va nearly as pale as that in AI. WGA-HRP injections, experiment #1325. **D**: The rostral insular cortex abutted the underlying claustrum (Cl) and its associated cortex. BDA deposit, experiment #1381.

Summary of Cortical Input to the Inferior Colliculus

A

CORTICAL AREA

MIDBRAIN TARGET	TONOTOPIC					NONTONOTOPIC					
	AI	AAF	P	VP	Ve	AII	EPD	EPI	Ins	Te	SF
CN	•	•					●	●			
DC I	•	•	•	•	•	●	●	•	•	●	
DC II	●	●	●	●	●	•	•	•		●	
DC III	●	●	●	●	●	•	•	•		●	
DC IV	●	●	•	•	●		•	•	•	●	
CC	●	●	●	●	●	●	•	•		●	•
LN	●	●	●	•	●	●	•	•		•	●
IcT		•		●		●	•	•		●	●
RP		•									●
SC						•	●		•		●
Sa	•	•	•	•		•	●	●	●	•	•
CG							•	•	●	•	
Cu									●		

Key
● heavy
● medium
• light

Comparison with Other Studies

B

CORTICAL AREA

MIDBRAIN TARGET	TONOTOPIC					NONTONOTOPIC						
	AI	AAF	P	VP	Ve	AII	EPD	EPI	Ins	Te	SF	multiple
CN								5				3
DC I	1 5	1				1		5	4c 5	4c 5		2 3 5 6
DC II	1 5	1				1		5	4c 5	4c 5		2 3 5 6
DC III-IV	1a 5a	1a				1b		5a	4c 5a	4c 5a		2a 3a 5a 6a
CC	1	1				1			5	5		2 3 5 6
LN	1 5a	1				1			5	5		2 3 5 6
IcT						1						3 5 6
RP											5	3 5 6
SC											5	2 5 6
Sa												2
CG												
Cu												

Key:

Study	Method	Notes:
[1]Andersen et al. (1980b)	Autoradiography; [3H]leucine	[a]Corresponds to their dorsomedial part of the central nucleus.
[2]Berman and Payne (1982)	Autoradiography; [3H]proline, [3H]leucine	[b]Corresponds to their medial part of the pericentral nucleus.
[3]Cooper and Young (1976)	Silver degeneration	[c]Interpreted from their text.
[4]Cranford et al. (1976)	Silver degeneration	
[5]Diamond et al. (1969)	Silver degeneration	
[6]Rockel and Jones (1973a,b)	Silver degeneration	

Figure 13

of which are associated with, if not actually a part of, the lateral tegmental system of the midbrain (Morest, 1965). Despite differences in projection density from tonotopic and nontonotopic fields, the collicular targets were similar in 7 of the 11 areas. These areas may differ so in physiological and functional organization, even within a subgroup (Neff et al., 1975; Clarey et al., 1992; Winer, 1992), that it is not clear what inferior colliculus process(es) could require their common input. The main exceptions are areas EPD, EPI, Ins, and SF. Areas EPD and EPI projected lightly throughout the caudal inferior colliculus and much more heavily rostrally (Fig. 8G,H). Areas Ins and SF had the most unusual patterns (Fig. 13). The insular cortex (Fig. 9) targeted the central gray heavily, suggesting cortical modulation of, and access to, autonomic ascending and descending circuits. Finally, SF corticocollicular input terminated exclusively in the lateral and rostral pole nuclei and in the superior colliculus (discussed further below). Such projection patterns would seem to be independent of tonotopy since the map of characteristic frequency in the lateral nucleus is not strikingly regular (Aitkin et al., 1975, 1981) despite the topographic arrangements of CC input to it (Figs. 4D, 8F). This result is in agreement with the idea that auditory afferents are more prevalent in the caudal inferior colliculus, and that polymodal and nonauditory projections are more prominent rostrally. This conclusion implies that the rostral pole may be affected by nonauditory input, while the central nucleus remains exclusively auditory.

Corticocollicular projections in other species

The concordance between studies in the rat and the present results is substantial, especially when different parcellations of cortical areas, the delineation of midbrain nuclei, and the specific sensitivity of the particular tracer are taken into consideration. Using WGA-HRP and a silver degeneration method, three patterns of CC projection were observed (Faye-Lund, 1985 [rat]). The central temporal cortex projected to the deepest two layers of the dorsal cortex; layer 1 of the dorsal cortex was the target of caudoventral temporal cortex, and the external collicular cortex (lateral nucleus) received input from the rostrodorsal temporal cortex. Only the first pattern had bilateral labeling, and this was near the intercollicular tegmentum. The strong input to the middle and deep layers of the dorsal cortex is consistent with the present results in the cat (Fig. 13A) and those from other studies (Fig. 13B). Subsequent studies injected *Phaseolus vulgaris*-leucoagglutinin (PHA-L) and BDA into the primary auditory cortex and revealed much the same global pattern of projection, and finer details as well (Herrera et al., 1994 [rat]). Deposits in the low- and high-frequency parts of Te1 (corresponding, presumably, to AI) produced modest labeling in the lateral nucleus and long strips of projections orthogonal to the layers of the dorsal cortex. The labeling abutted, or even extended into, the central nucleus. The central nucleus was labeled more extensively by injections in the dorsal part of Te1; deposits in the latter subarea did not produce a topographic distribution of labeling like those in ventral Te1. These patterns are in close accord with the present results. Another PHA-L study showed a similar nuclear pattern, and claimed that the central nucleus is also a cortical target, regardless of the cytoarchitectonic scheme used (Saldaña et al., 1996 [rat]). The differences between studies in defining the central nucleus nevertheless remains an unresolved issue (compare, for example, Herbert et al. [1991 (rat)], their Fig. 2, and Saldaña et al. [1996], their Fig. 11, inset). Further studies have concluded that there is little or no cortical input to the central nucleus (Druga et al., 1997 [rat]). Experiments using BDA revealed a projection by fine axons with small boutons in the central nucleus (Winer, unpublished observations: Table 1 [cat]) after deposits in some cortical regions. In the most dorsomedial part of the central nucleus the input was much stronger (Figs. 3D, 4D) and was revealed by both tracers.

In primates, tritiated amino acids injected in auditory cortex labeled terminals mainly in the pericentral nucleus and in the central nucleus (FitzPatrick and Imig, 1978 [owl monkey]). The latter projection from area AI (their Fig. 11B: 6) was similar to experiments after cat AI injections (present results, Fig. 3D). The discrepancy with regard to the central nucleus could reflect differential architectonic interpretations since more conservative estimates of its limits in a new world primate showed a modest central nucleus projection, more extensive bilateral input, and much heavier labeling in the lateral or external nuclei (Luethke et al., 1989 [tamarin]).

Implications for subdividing the inferior colliculus

At least four auditory regions are usually recognized in the inferior colliculus and associated midbrain. These are the central nucleus, the dorsal (and perhaps the caudal) cortex, the lateral nucleus, and the intercollicular tegmentum. They differ in their neuronal architecture, afferent and efferent connections (including their CC projection), and physiological organization (Aitkin, 1986).

There is some accord among the different views (Rockel and Jones, 1973a,b; Morest and Oliver, 1984; Oliver and Morest, 1984; see also Geniec and Morest, 1971) with regard to the principal divisions (such as the central nucleus, dorsal cortex/pericentral nucleus, lateral nucleus/external nucleus), even if the precise boundary of each division varies among studies. However, further consensus with respect to finer architectonic subdivisions has been no easier to achieve here than elsewhere in the neuraxis (Lashley and Clark, 1946). Our data support categorically

Fig. 13. Summary of cat corticocollicular (CC) connections (A) and comparison with other studies in this species (B). **A**: Origins (top) and targets (left side) of CC projections. Dot size is proportional to the strength of the ipsilateral projection; it represents a qualitative assessment of labeling intensity and breadth in a nucleus (see Key). The values were derived from the experiments illustrated here. There was a disjunction between the distribution of labeling from TONOTOPIC and NONTONOTOPIC areas. The main distinctions were 1) stronger TONOTOPIC projections and 2) more divergent NONTONOTOPIC labeling. Parallels included 1) the relative paucity or absence of terminals in the central nucleus, 2) the concentration of labeling in the caudal half of the inferior colliculus, and 3) the divergence of projection from all but one architectonic field. **B**: A summary of findings from previous studies of cat corticocollicular projections. The principal studies used autoradiographic or axonal degeneration methods to reveal CC projections (see Key). With regard to nuclear targets, there is a close concordance between the present results and prior work. The chief differences are 1) the expanded perspective on auditory cortical input to extraauditory midbrain centers such as the central gray, 2) the revised estimate of the insular cortex (Ins) contribution to the CC system, and 3) an enhanced view of the parallels in patterns of CC projection from tonotopic fields and their contrasting role in descending control of the midbrain.

a more refined parcellation of the inferior colliculus (Morest and Oliver, 1984; Oliver and Morest, 1984). In some nuclei even further subdivision may be warranted. For example, the lateral nucleus receives differential patterns of CC input to its lateral and medial subregions (compare Figs. 3D, 7D), areas that appear to be distinct architectonically as well.

The central nucleus has well-developed fibrodendritic laminae (Oliver and Morest, 1984). Much of its ascending input comes from the cochlear nucleus (Osen, 1972) and the olivary nuclei (Adams, 1979), and it projects primarily to the ventral division of the medial geniculate body (Kudo and Niimi, 1980), preserving the topography of input imposed upon it by the medullary auditory nuclei, and receiving at most a modest CC projection (Fig. 13A). Single neurons have sharp tuning curves and high Q_{10} dB values and both their processes and many of the subcollicular afferents to them are arranged in isofrequency laminae (Aitkin et al., 1975), which may be the functional correlate of the fibrodendritic lamination (Oliver and Morest, 1984). The modest CC projection to the central nucleus is enigmatic and suggests that there is little in the way of monosynaptic cortical influence in much of the central nucleus.

Less is known about dorsal cortex organization, although these neurons have a laminar arrangement (Oliver and Morest, 1984). Input from the tonotopic areas was robust and ended primarily in layers II–IV and with lighter layer I labeling. Although its projection from the cortex is substantial (Diamond et al., 1969; present results), there is little or no brainstem input to layers I–III (reviewed in Irvine, 1986). This argues that the substantial neocortical projection can influence structures that are independent of ascending information. Although the dorsal cortex projects mainly to the dorsal nucleus of the medial geniculate body (Calford and Aitkin, 1983), many cells also project in the commissural system linking the inferior colliculi (Aitkin and Phillips, 1984). Response properties of dorsal cortex cells are heterogeneous. The neurons prefer complex stimuli and have multipeaked tuning curves far broader than those in the central nucleus. This is certainly consistent with the massive areal convergence (present results), the virtual absence of subcollicular projections and the range of physiological patterns represented by the different cortical inputs. The tonotopic organization, if any, is uncertain (Aitkin et al., 1975, 1994) and the role of the dorsal cortex is obscure. It remains to be seen whether ascending (Calford and Aitkin, 1983) and descending (Hashikawa, 1983) tectofugal neurons are each targets of corticofugal input. The affiliations of the caudal cortex are also unclear because little is known of its physiology or connections.

The lateral nucleus has no laminar suborganization, and its neuronal population is diverse in size, shape, and dendritic configuration (Morest and Oliver, 1984). Input arises from the central nucleus and the dorsal column and spinal trigeminal nuclei (Aitkin et al., 1981), suggesting an auditory and somatic sensory role. It projects mainly to the medial division and deep dorsal nucleus of the medial geniculate body (Calford and Aitkin, 1983), which are outside the classical auditory pathway (Winer and Morest, 1983a). Corticofugal input is light to moderate and arises from all areas but one. About two-thirds of the cells respond to auditory stimuli, and they have broad afferent tuning. A few neurons are polysensory (Aitkin et al., 1981).

Neurons in the intercollicular tegmentum have long, predominantly smooth dendrites and they receive both spinal and nonauditory corticofugal input (RoBards et al., 1976 [opossum]) and auditory cortical projections (present results). Like the caudal and dorsal cortices, little is known of its physiological organization (Aitkin, 1986).

The themes that link the dorsal cortex, lateral nucleus, and intercollicular tegmentum are that their principal auditory inputs appear to be of cortical (present results) and of intrinsic or commissural origin (Aitkin and Phillips, 1984), and that the tonotopic fields have the strongest and most focal projections (except for the intercollicular tegmentum). Since these collicular subdivisions have strong tectopontine projections (Hashikawa, 1983), a prospective role for the cerebral cortex is corticopontocerebellar feedback that might be useful in tasks such as passive sound localization and cross-modal integration. Since the auditory corticofugal projections to the superior colliculus arise from only two nonprimary fields, this suggests that the descending auditory influence on the visual midbrain is modest.

Cortical effects on collicular function

Neurons in the cochlear nucleus, the central nucleus of the inferior colliculus, and the ventral division of the medial geniculate body share many of the same physiological attributes, such as fidelity to the stimulus, comparable sharp tuning, and exclusively auditory responsiveness, to name just a few dimensions (Aitkin, 1986; Irvine, 1986; Clarey et al., 1992). These neurons represent the lemniscal pathway (Winer and Morest, 1983a). This continuity suggests that areas with sharply (or similarly) tuned neurons are likely to be interconnected and that such connectivity may extend to the corticofugal system as well. In fact, the ventral division receives a massive and topographic and reciprocal corticothalamic input from AI (Diamond et al., 1969). This principle is violated, however, by the strong input to the dorsal cortex and lateral nucleus and the weak projection to the central nucleus from AI. This suggests that the cortex exerts differential effects on its postsynaptic targets, that only a comparatively limited part of the midbrain requires monosynaptic corticocollicular input (Fig. 14A–C: 2), and that the preservation of topographic relations is not a determinative feature, at least in the CC system.

The physiological effects evoked in the inferior colliculus by stimulating the cerebral cortex include excitatory postsynaptic potentials, inhibitory postsynaptic potentials, and sequences combining these in the cat (Mitani et al., 1983) and rat (Syka and Popelár, 1984). Some elegant studies of CC function in echolocating bats revealed that the cortex continuously affects the output of single collicular neurons by enhancing threshold, attenuating unit response area, and improving sharpness of tuning (Sun et al., 1996 [big brown bat]). Stimulating delay-tuned corticocollicular neurons facilitated the discharge of similarly tuned inferior collicular neurons, suggesting a critical role in the midbrain for cortical feedback in temporal processing. Pharmacological inactivation of the cortex had complex effects, such as enhancement of the response in some cell classes for extended periods; this suggests that the consequences of CC activation are diverse (Yan and Suga, 1996 [mustached bat]). Cortically mediated focal excitatory feedback or broadly distributed lateral inhibition may last for ~2 hours (Zhang et al., 1997 [mustached bat]). In

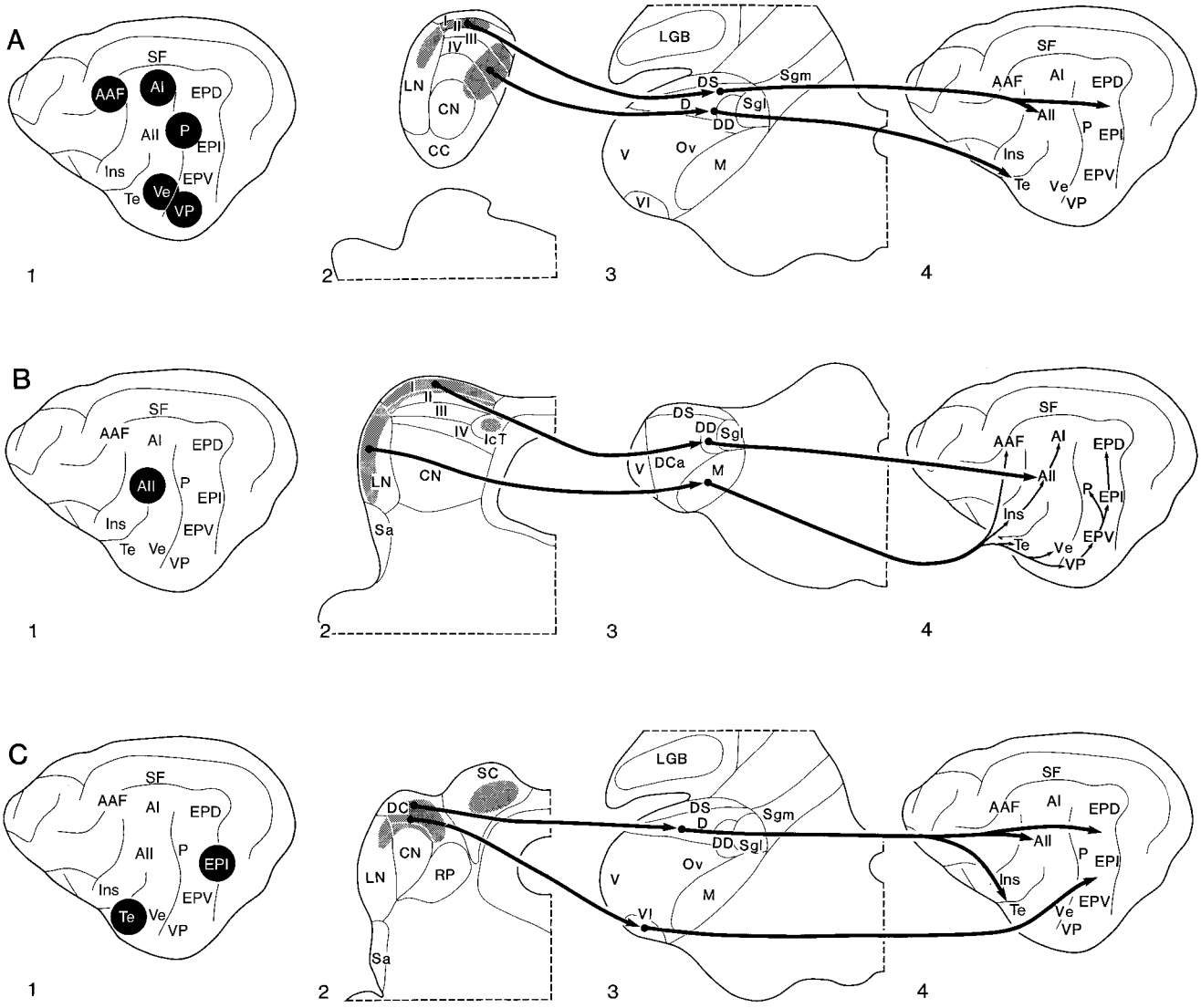

Fig. 14. Interrelations between the corticocollicular origins (1) and their midbrain targets (2), and some hypothesized relations to the auditory thalamus (3) and the thalamocortical system (4). This is not intended as a summary of results; its aim is to show how CC input could affect parts of the inferior colliculus with connections to the medial geniculate body. **A**: The tonotopic cortical areas project convergently onto several inferior collicular subdivisions. These midbrain nuclei project to auditory thalamic nuclei that influence nontonotopic auditory fields selectively, such as areas AII or Ins. AII receives input from AI (Winguth and Winer, 1986) and projects to area P (Rouiller et al., 1991). This could provide reentrance for nontonotopic thalamic projections to influence tonotopic fields. Descending tectofugal pathways are omitted. 1, figurine of the lateral neocortex showing the regions injected (black circles); 2, the ensuing corticocollicular labeling (stippled) on a transverse section; the main foci of anterograde input are the lateral nucleus (central part) and the dorsal cortex (superficial and deep sectors); 3, tectothalamic projections (heavy black lines) from the labeled midbrain territories terminate (arrowheads) mainly in the dorsal division nuclei in the medial geniculate body (Andersen et al., 1980a; Calford and Aitkin, 1983); 4, the cortical projection targets of the dorsal division are preferentially to nontonotopic, nonprimary areas. **B**: The corticocollicular projection from area AII, a nontonotopic region with extensive, divergent corticocollicular input to the superficial dorsal cortex, lateral nucleus, and intercollicular tegmentum. These collicular subdivisions have two parallel tectothalamocortical projections, one focal and the other divergent. Nontonotopic midbrain centers could thus influence both tonotopic and nontonotopic areas. 1, area AII has little topographic physiological organization, and it is the origin of divergent CC projections (Fig. 13A); 2, the superficial dorsal cortex (layer I) projects to the deep dorsal nucleus in the auditory thalamus, and the lateral nucleus sends fibers to the medial division; 3, these two thalamic nuclei have different patterns of cortical projection; 4, the deep dorsal nucleus projects mainly to area AII (Winer et al., 1977), and the medial division projects to many auditory and nonauditory areas, only some of which are shown here (Niimi and Matsuoka, 1979). AII corticocollicular projections thus activate specific, focal midbrain pathways whose influences ultimately reach thalamic sites that project divergently to the cortex. **C**: Corticocollicular projections of temporal cortex (caudal to the pseudosylvian sulcus) link the rostral inferior colliculus with auditory thalamic nuclei in the dorsal division, which in turn project widely to nonprimary auditory cortex (Winer et al., 1977). 1, the temporal cortex has strong input to the deep layers of the dorsal cortex; 2, the output of the rostral dorsal cortex reaches two auditory thalamic targets: the dorsal and the ventrolateral nuclei; though separate spatially, both are part of the dorsal division (Winer et al., 1977); 3, projections from the dorsal and ventrolateral nuclei reach many nonprimary cortical areas, especially those without tonotopic organization (Winer, 1992). The main conclusions are: 1) each cortical area projects divergently to several inferior collicular nuclei; 2) each IC nucleus receives convergent input from several areas; 3) the IC targets of this input project to the nonprimary nuclei of the medial geniculate body, or 4) send descending projections to the pons or related midbrain premotor centers (not shown); and 5) the auditory thalamic nuclei that are part of the corticocolliculogeniculate pathways project divergently to wide territories of nonprimary auditory and associated polysensory cortex. The input to the superior colliculus may help to coordinate auditory and visual premotor signals for spatial orientation. See Discussion for further analysis.

the big brown bat (*Eptesicus fuscus*), stimulation and iontophoretic studies using γ-aminobutyric acid (GABA) found that corticocollicular activation elevated inferior colliculus neuron thresholds and reduced their sensitivity, decreased unit spatial response areas, and thereby sharpened spatial tuning, and increased Q_{10} dB values to improve tuning (Sun et al., 1990). It remains to be discovered which processes are established by the cerebral cortex in the inferior colliculus and which postsynaptic midbrain neurons mediate them. It is uncertain whether these changes might affect the midbrain neurons that project to the medial geniculate body. By the same token, the tectofugal projections of the lateral nucleus to the cochlear nucleus, pontine nuclei, and periolivary regions (Hashikawa, 1983; see also Huffman and Henson, 1990) suggest that parallel descending pathways exist whose functional impact is also unknown. Perhaps these projections are as specific (given their different origins) and as different (given the variety of the targets) as those in the ascending auditory system.

The suprasylvian fringe (SF) cortical projection underscores the prediction that the effects of CC activation may have diverse physiological roles. Thus, SF neurons have wide, often multipeaked response profiles (Middlebrooks and Zook, 1983; Sutter and Schreiner, 1991), and >80% of those with long latencies were duration selective (He et al., 1997). This suggests that SF neurons prefer complex stimuli and represent physiological events with broad temporal profiles. It would be interesting to know the targets of the SF projections (Figs. 11, 13A) in bats (Casseday et al., 1994) and whether analogous projections of pallial origin exist in the amphibian (Feng et al., 1990) auditory midbrain, especially since they represent a unique pattern in the present study (Fig. 13A). The long latencies of cat SF neurons may play a role in the complex motor adjustments required for sound orientation in space, a process in which the lateral nucleus, intercollicular tegmentum, and superior colliculus appear to be essential elements (Aitkin, 1986; Huffman and Henson, 1990). In any event, the midbrain effects of AI or SF stimulation are unlikely to be the same.

Because of the different auditory affiliations of the dorsal cortex and the lateral (external) nucleus relative to the central nucleus, the tectopontine projection may have an acousticomotor, rather than an exclusively auditory, role. Dorsal cortex lesions affect vigilance and attention rather than producing specific auditory deficits (Jane et al., 1965). This system might be analogous to the visual corticotectal projection and the massive tectofugal systems devoted to the control of eye and head movements rather than the pathways subserving form or color vision (Huerta and Harting, 1984).

Can the auditory neocortex interact across modalities or influence motor behavior? This possibility is consistent with the idea of a corticofugal influence onto the striatum (Reale and Imig, 1983) as well as the visual and auditory midbrain. This could affect premotor neurons before movement, much like the long polysynaptic loops involving the inferior colliculus (Casseday and Covey, 1996). The corticostriatal and corticocollicular systems may provide complementary feedback to premotor and brainstem sensory centers that require an auditory frame of reference. These corticofugal subsystems still need to be compared and contrasted more rigorously.

Corticocolliculothalamocortical influences

Descending auditory projections seem to have considerable influence on the ascending limb of the auditory system, from olivocochlear to corticocochlear projections, to name just two examples. The dorsal cortex, lateral nucleus, and intercollicular tegmentum each project to the pontine (Kawamura, 1975) and cochlear (Kane and Finn, 1977) nuclei. Even the cochlear nucleus receives projections from primary auditory cortex (Weedman and Ryugo, 1996b [rat]). These axons synapse on cochlear nucleus granule cell dendrites, implying a modulatory role in cochlear nucleus function (Weedman and Ryugo, 1996a [rat]). Cochlear nucleus operations must therefore be modulated by corticofugal and tectofugal input. It remains to be seen whether collicular Golgi type II cells are themselves the target of CC input.

It is not clear how the auditory corticocollicular projections might affect the ascending auditory system since simultaneous recordings from inferior colliculus and medial geniculate body neurons while stimulating the auditory cortex are not yet available. Absent direct evidence, the possible connections between neurons in the corticocollicular and colliculothalamic systems might offer clues salient to function. To explore this idea more formally, Figure 14 traces the projections from sets of cortical areas (Fig. 14: 1, black circles) to particular inferior colliculus subdivisions (Fig. 14: 2, stippled). Each row represents a different terminal pattern of cortical input onto midbrain targets, and only three patterns are presented. The tectothalamic cells of origin (Fig. 14: 2, small black dots) project to the auditory thalamus (Fig. 14: 3, arrowheads), whose neurons terminate in auditory cortex (Fig. 14: 4, arrowheads). The CC projections of area AII (Fig. 14B) and their ensuing redistribution through the tectothalamocortical system provide a test for the present approach. The AII deposits label a more or less continuous ring along the perimeter of the lateral nucleus and in layers I–II of the dorsal cortex (Fig. 7). The restricted spatial domain of the corticocollicular projection belies its subsequent divergence in the thalamus: dorsal cortex layer I neurons target the deep dorsal nucleus of the medial geniculate body (Calford and Aitkin, 1983). These neurons project back to area AII, thus completing the loop (Niimi and Matsuoka, 1979). In contrast, the lateral nucleus (Fig. 14: 2, LN) targets mainly the medial division of the medial geniculate body (Kudo and Niimi, 1980), which then projects divergently onto every area of auditory cortex (Winer et al., 1977) and to the amygdala (Shinonaga et al., 1994).

Perhaps the corticocollicular projection from area AII to the dorsal cortex and the lateral nucleus acts as a hub to exert (or at least enable) powerful widespread, influences on extralemniscal thalamic nuclei (Winer and Morest, 1983a). These nuclei might activate two thalamocortical circuits with complementary effects (Fig. 14B: 3, DD, M). The first is a pathway from the deep dorsal nucleus (Winer and Morest, 1983b) to AII (Winer et al., 1977). This projection might play a part in two functions: 1) by activating the corticofugal input to the dorsal collicular cortex (Fig. 14B: I) it could sustain transmission in the corticotectothalamocortical pathway to AII for processes requiring extended analysis, such as detecting signals embedded in noise (Neff et al., 1975); 2) the lateral nucleus pathway to the medial division (Fig. 14B: 2, LN; Fig. 14B: 3, M) could drive polysensory medial division neurons

(Wepsic, 1966), which are capable of long-term potentiation (Gerren and Weinberger, 1983) and which terminate in cortical layers I and VI (Niimi and Naito, 1974) and project to the limbic forebrain (Shinonaga et al., 1994). The medial division pathways may have a role in mediating plasticity in the thalamocortical system (Weinberger, 1982) or in routing auditory influences to the appropriate autonomic centers via the thalamoamygdaloid system (LeDoux et al., 1984 [rat]), respectively. The corticofugal input to the central gray provides access to ascending and descending limbs of the medullary autonomic and nociceptive networks that could facilitate aversive responses to sound.

A further potential effect arises from tectothalamocortical influence on a segment of the corticothalamic system. Area AII (among others) is a source of large corticothalamic axon terminals in the dorsal division (Bajo et al., 1995). The role of these terminals on auditory thalamic physiological events is unknown. However, analogous somatic sensory corticothalamic projections to the rat posterior thalamus can check the transmission of information through the extralemniscal nuclei (Diamond et al., 1992). It may seem implausible to invest the corticocollicular system with so many prospective roles in the thalamus and cortex, not to mention those in subcollicular centers. Nevertheless, the variety, complexity, and logic of corticocollicular and corticothalamic connections are consistent with this idea. The case can be made that the other corticocollicular projections might affect polymodal processing (Fig. 14A) and auditory-limbic relations (Fig. 14C).

Speculations on the function of the corticocollicular system

Theories of the role of the CC system are limited by lack of knowledge about how cortical input affects inferior colliculus neurons. Although physiological studies can reveal the effects of stimulating the auditory cortex on collicular target neurons, these cells are neither the ultimate target nor the final common pathway prior to sensorimotor integration or the direct activation of motoneurons. It is tempting to compare the CC system with the primate corticospinal system, whose projections terminate mono- or (more commonly) disynaptically onto motoneurons (Phillips and Porter, 1977; Canedo, 1997) and exert their effects onto muscle rapidly. However, such a comparison is misleading since the auditory CC system is entirely premotor in several ways. First, the CC projections have relatively direct access to pontine and other precerebellar neurons; however, these cells are remote synaptically from lower motoneurons. The analogous point can be raised for the reentrant (CC) segment of the corticotectothalamocortico-tectal loop: its polysynaptic affiliations and divergent projections to the neocortex make it a dubious candidate for a temporally rapid (Casseday and Covey, 1996) or modality-specific (Huffman and Henson, 1990) functional role. The third piece of evidence against a direct or executive role for the CC system is the size and distribution of its axon terminals as seen in the BDA material (unpublished observations). The boutons are predominantly small or medium-sized, granular in form, and prominent in the neuropil. They do not appear to end in appreciable numbers on neuronal somata, and they may thus form axodendritic synapses. Finally, the massive CC convergence onto relatively few collicular nuclei is entirely unlike the highly conserved topography of the descending motor system.

These speculations entail predictions that might be examined experimentally. For example, cortical influence on the fine temporal control of inferior collicular neuronal discharge patterns needs to be explored more fully in the cat with stimulation/inactivation experiments. It also remains unclear how the temporal regulation of inferior colliculus neurons' physiological behavior, which certainly reflects the precision of brainstem input, would be altered by CC projections (Glendenning and Masterton, 1983; Oliver, 1984; Irvine, 1986).

Among the biologically plausible hypotheses for the CC system are 1) as influences on vigilance and attention (Jane et al., 1965); 2) to provide reafference to the midbrain about the global (but not the virtual) location of sound in space to help track targets in motion or modulation (Middlebrooks et al., 1994); 3) as an upstream arbiter for control of audiospinal reflexes (Wright and Barnes, 1972); or 4) as a source for tonic feedback (like that from the premotor nuclei) or of feedforward signals (toward the thalamus and cortex) for ongoing behavior such as tracking and assessing biologically meaningful stimuli embedded in ambient noise (Bregman, 1990). These possibilities are not mutually exclusive, and each could be valid. There are also parallels between the auditory corticopontocerebellar system and the projection from the visual cortex to the superior colliculus. The latter system has a comparable set of components, including a descending premotor element (the tectospinal tract) and a reentrant segment (the corticotectopulvinar pathway) whose projection to parietal cortex (Niimi et al., 1974; Updyke, 1977) resembles the tectothalamocortical divergence that is a cardinal feature of the auditory forebrain (Fig. 14A–C: 3,4). These ideas suggest that the study of the corticocollicular system is poised to enter a new phase in which the organizing principles that constrain it can be compared critically with those of other sensorimotor circuits.

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